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THE PROHYPERTENSIVE AND ANTIHYPERTENSIVE ACTIONS OF THE KIDNEY *

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THE role of the kidney in experimental renal hypertension—and probably also in human renal hypertension—is twofold. On the one hand, it has a prohypertensive action mediated by the release into the blood of a pressor substance, renin, which, by acting on a serum α-globulin, produces "angiotensin," an octapeptide with potent vasoconstrictor and pressor actions.

On the other hand, the normal kidney tissue exerts some kind of antihypertensive action the exact nature of which is still unknown.

This dual and contrariwise role is not unique in the organism. For instance, the adrenal cortex secretes hormones which may have opposite actions on inflammation in certain experimental conditions, leading Selye [1] to classify them as prophlogistic and antiphlogistic. If a similar situation existed for the kidney, one could hypothesize a substance which, unlike renin, serves to maintain the normal blood pressure. Such is Grollman's hypothesis.[2]

But the situation may be more complex, the appearance of hypertension, and perhaps also the liberation of renin by the kidney, being determined by the relation between certain demands imposed by the organism upon the kidney and its capacity to respond to them, a situation which has greater similarity to the relation between ACTH and the adrenals, or thyrotropin and the thyroid gland.

THE PROHYPERTENSIVE ACTION OF THE KIDNEY

Let us first consider the prohypertensive action of the kidney.

In 1934 Goldblatt and his collaborators [3] published a method for the

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production of chronic hypertension in the dog (figure 1). Partial compression of both renal arteries caused a rise of systolic and diastolic blood pressure, not necessarily accompanied by renal excretory insufficiency, without changes in heart rate and output and with an increase in peripheral resistance—in summary, a type of hypertension which reproduces with much fidelity some of the distinctive characteristics of human essential hypertension.

Goldblatt's discovery dissipated all doubts which still existed about the relation between the kidney and arterial hypertension, a relation already postulated by Bright [4] in 1836.

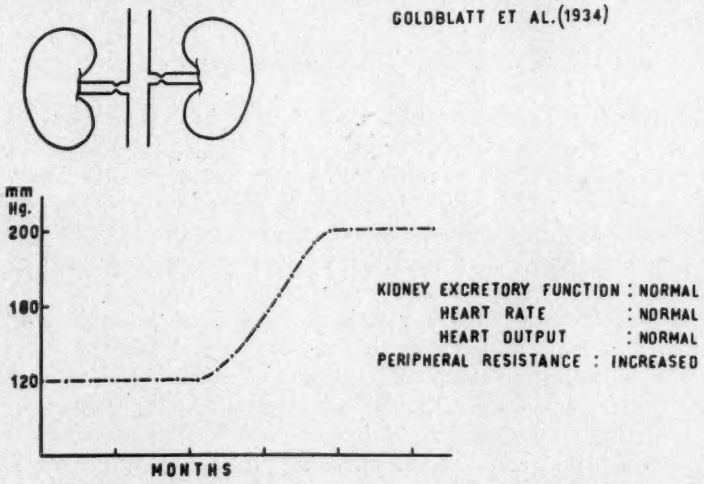

FIG. 1. Diagrammatic representation of results of partial compression of both renal arteries.

Many workers contributed to the study of the mechanism of this type of experimental hypertension. Investigations made in our country by Houssay and Fasciolo [5] (figure 2), grafting the ischemic kidney to the neck of a nephrectomized dog, showed first that the mechanism was humoral, and then (figure 3) that the ischemic kidney liberated renin into the blood.[6, 7] Renin does not have a direct pressor action, but acts upon a serum α-globulin (which we called hypertensinogen), giving rise to the formation of a new substance with vasoconstrictor and pressor action which we called hypertensin. At about the same time Page and his collaborators, Helmer and Kohlstaedt,[8, 9] following a completely different approach, arrived at similar conclusions and called their active substance "angiotonin." In a meeting held last July in Ann Arbor, celebrating the twenty-fifth anniversary of Harry Goldblatt's epochal discovery, the fusion of both denominations into a hybrid was suggested, and Page and I have agreed in proposing the term "angiotensin." [10] This proposition, if accepted by all workers in the field,

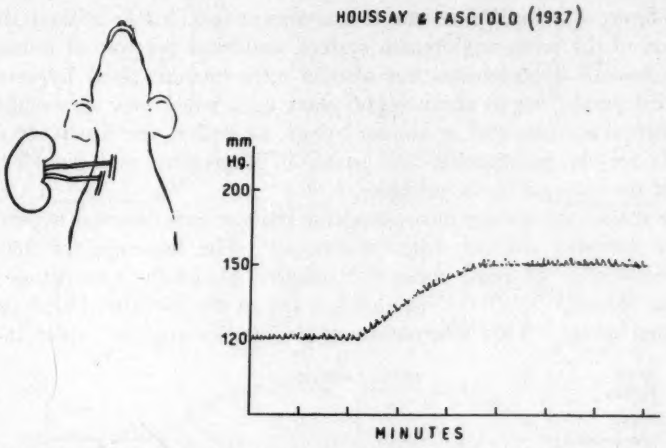

FIG. 2. The graft of an ischemic kidney from a renal hypertensive dog into the neck of a nephrectomized dog causes a rise of blood pressure in the latter, showing that the ischemic kidney liberates a pressor substance into the blood.

will eliminate the possible confusion arising from a double nomenclature for a single substance. If the new name is not adopted it will of course only aggravate the present state of affairs.

In the many years which have elapsed since the discovery of experimental renal hypertension and of the renin-angiotensin system, three periods may be demarcated. The first comprises the years 1936 to 1942, when the mentioned discoveries, the novelty of the subject and especially its possible practical clinical applications attracted many workers to the field. But when the hopes as to the rapid application of the new knowledge to the pathogenic diagnosis and treatment of human hypertension did not rapidly materialize, interest in the subject, and with it the number of papers pub-

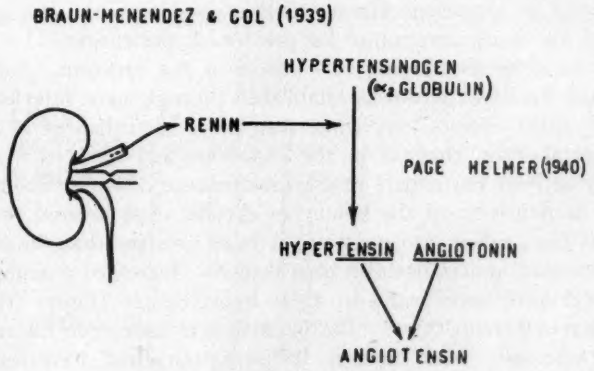

FIG. 3. For explanation see text.

lished (figure 4), diminished and it was almost fashionable to deny the participation of the renin-angiotensin system, and even the role of kidney, not only in human hypertension but also in experimental renal hypertension. The third period began about eight years ago, when new observations in experimental animals and in human beings, as well as the discovery of new methods for the purification and isolation of proteins and peptides, have renewed the interest in the problem.

The role of the kidney in nephrogenic chronic experimental hypertension is again accepted without much discussion. The loosening of the clamp which constricts the renal artery [11-16] (figure 5), or the extirpation of the ischemic kidney,[3, 5, 13, 17, 18, 19] produces a fall of the elevated blood pressure to normal levels. This affirmation needs further analysis, since its truth

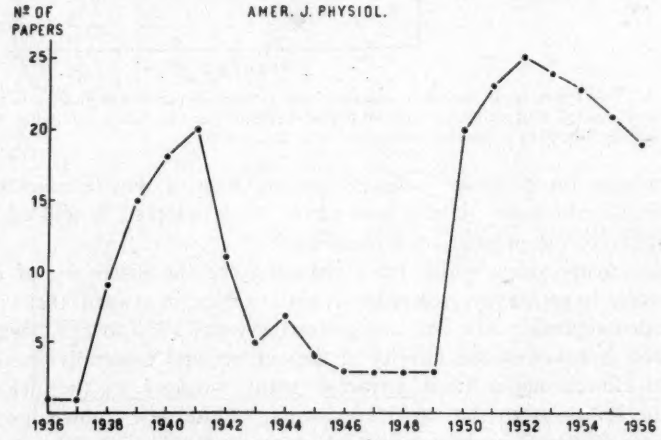

FIG. 4. Number of papers published in the *American Journal of Physiology* on experimental renal hypertension and the renin-angiotensin system during the period 1936–1956.

is conditioned by numerous factors such as type of renal damage, animal species and, above all, duration of the previous hypertension. I cannot possibly now consider thoroughly this aspect of the problem. Suffice it to say that once the hypertension is established through some interference with the kidney, other factors may come into play: disturbances in the water and salt metabolism, changes in the endocrine and nervous system, etc., which may actively participate in the maintenance of hypertension.

If the participation of the kidney in chronic experimental renal hypertension has been called into question, it is no wonder that the role of the renin-angiotensin system has also been denied. Increased amounts of renin in the blood have been found in acute hypertension (figure 6), whether experimental or human.[20, 21, 22] But in chronic hypertension the results have been contradictory. Most authors, including ourselves, have found no increase in the concentration of renin in the blood of chronically hypertensive

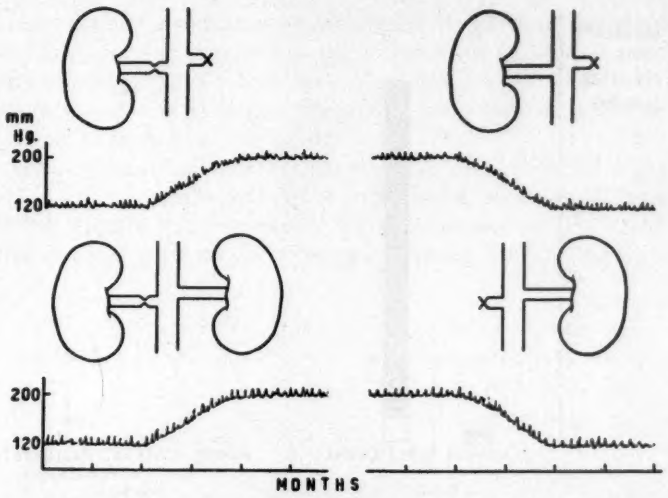

FIG. 5. The loosening of the constricting clamp which constricts the renal artery or the extirpation of the ischemic kidney produces a fall of the elevated blood pressure.

animals [21, 24, 25, 26, 27] or patients.[24, 26, 28, 29] But it must be recognized that these negative results cannot be considered independently from the methods used, which up to now have been deficient in sensitivity and specificity. The positive results obtained by Skeggs et al.[23, 30, 31] carry much more weight. They found increased amounts of angiotensin in the blood of chronically hypertensive dogs and of patients with malignant hypertension (figure 7).

We have recently devised a method for the estimation and assay of angiotensin in blood. The advantages of our method are its specificity, its high rate of recovery (about 100%), its relatively high sensitivity (0.01 Goldblatt unit per liter), the small size of the blood sample (50 ml.), and the possibility of making identification tests even when the concentration of angiotensin is only 0.03 Goldblatt U./L. Experiments are now in progress

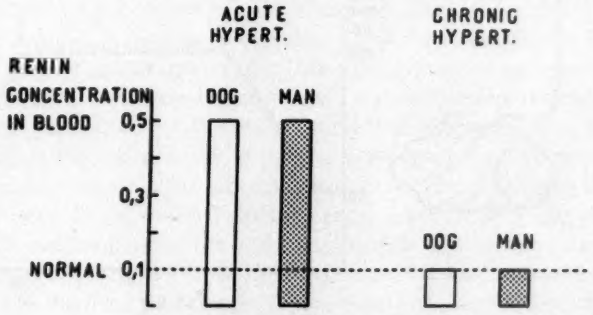

FIG. 6. For explanation see text.

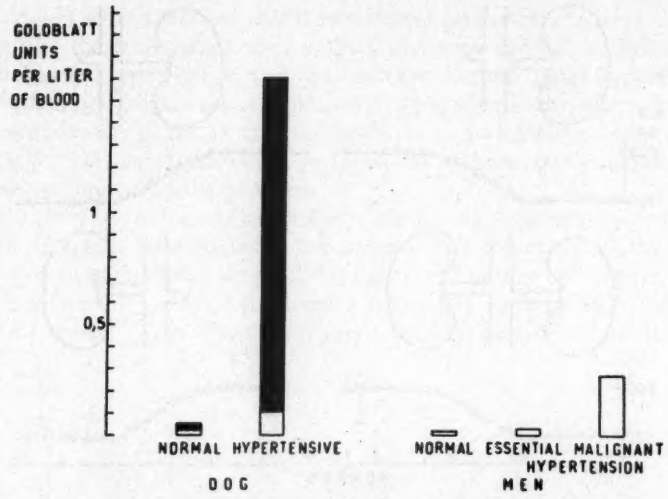

FIG. 7. Concentration of angiotensin (Goldblatt units) in the blood of hypertensives.

in which the estimation of angiotensin in blood is made under different physiologic and pathologic conditions.

Apart from the demonstration by Skeggs et al. of an increased amount of angiotensin in the circulating blood of hypertensive dogs and human beings with malignant hypertension, other indirect evidence confirms the participation of the renin-angiotensin system in the genesis of experimental renal hypertension:

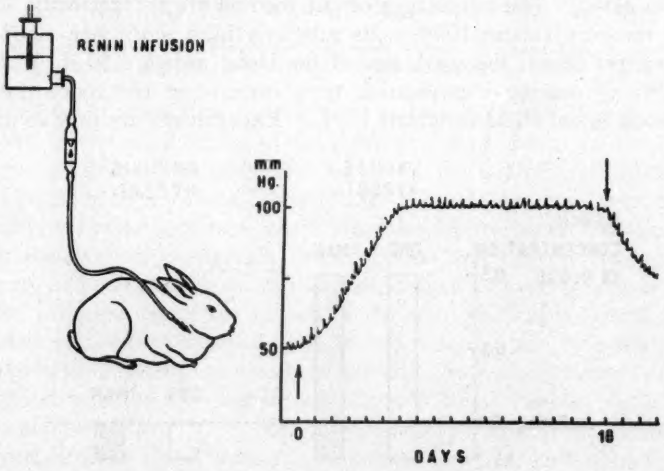

FIG. 8. Hypertension in rabbit from infusion of renin (see text).

1. Infusions of renin into rabbits (figure 8) produce hypertension that is maintained for the duration of the infusion up to 18 days, renin being the only substance with which such a result could be obtained.[32] (Now that large amounts of synthetic angiotensin are available, a similar experiment should be done with this substance.)

2. The repeated injection of heterologous renin into the dog produces antibodies to dog renin and lowers the blood pressure in hypertensive dogs[33, 34, 35] (figure 9), or prevents the development of experimental renal hypertension in dogs, both effects being correlated with the plasma antirenin levels.

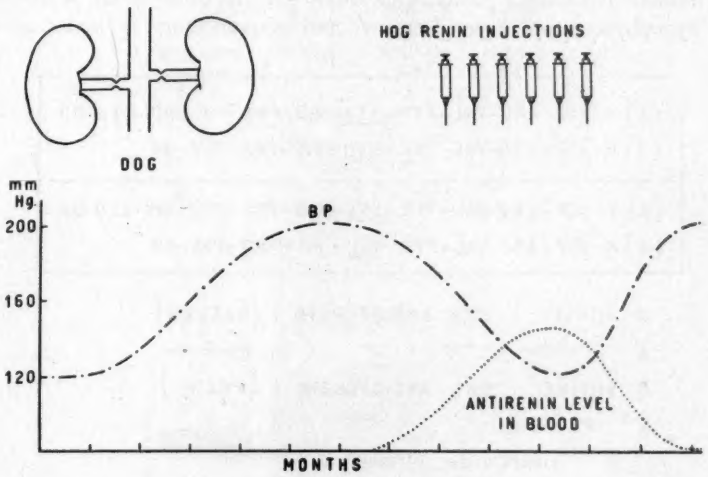

FIG. 9. For explanation see text.

Recently angiotensin has been obtained in pure form, and its structure recognized[36, 37] and finally synthesized.[38, 39] Two forms of angiotensin have been purified: angiotensin I, an inactive decapeptid which, by the action of a plasma enzyme, is converted into the octapeptide, angiotensin II, the most powerful pressor material known. According to the angiotensinogen from which it is derived (horse or ox serum) a difference in structure has been recognized (figure 10). We have found evidence suggesting that angiotensin may be one of a family of pressor polypeptides which may be formed in the organism by renin or other proteolytic enzymes.[40]

All this is, to me, overwhelming evidence in favor of the participation of humoral mechanisms of the renin-angiotensin type in the genesis of renal experimental hypertension and of at least malignant human hypertension, and I foresee that the therapeutic application of the newer knowledge which I have outlined is not too far off.

The Antihypertensive Action of the Kidney

Let us consider now the second aspect of the participation of the kidney in hypertension: its antihypertensive or protective action.

During the last 12 years I have followed a line of research under a working hypothesis which may be expressed as follows [41]: The size of the kidney and its functional capacity, which under normal conditions are closely connected, are regulated by the concentration in the blood of a substance, renotrophin, which is probably some by-product of protein metabolism. The rate of production of renotrophin increases under the influence of the hormones of the pituitary gland, the thyroid and the masculine gonads, as well as in animals fed with a protein-rich diet. On the other hand, it decreases after hypophysectomy, thyroidectomy, and gonadectomy in males as well

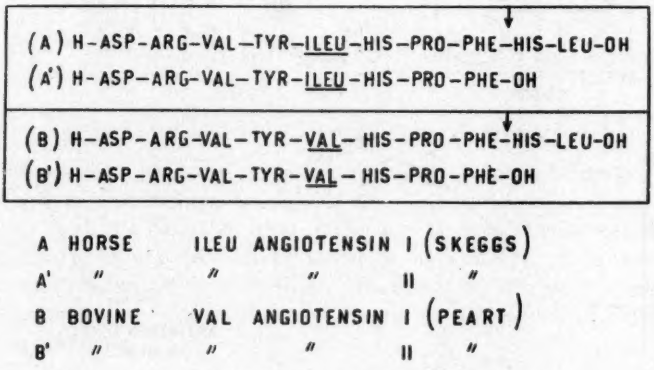

FIG. 10. Structure of angiotensin.

as in animals fed a protein-poor diet. Its concentration in blood would depend on the equilibrium between the rate of renotrophin formation and its destruction or utilization by the kidneys (figure 11). In normal conditions, an increase in the rate of production of renotrophin causes renal hypertrophy and hyperfunction; a decrease, renal atrophy and hypofunction. Unilateral nephrectomy would cause a transitory rise in the blood level of renotrophin until a new equilibrium is reached, due to the growth in size and function of the contralateral kidney. But when the kidney is unable to respond to renotrophin with an increase in size and function because its growth is impeded by mechanical or pathologic hindrances, hypertension develops (figure 12).

It is well known that practically all methods used for the production of experimental renal hypertension involve a reduction in the amount of functional renal tissue.

According to our hypothesis, the blood pressure of animals with reduction of renal mass should increase to higher levels or, if hypertension is

still absent, it should appear if (1) the rate of production of renotrophin is increased, or (2) the functional renal mass is further reduced (figure 13). This second corollary is of common occurrence and has been repeatedly verified. As to the first one, we have shown that the administration of somatotropin,[42] thyrotropin in the presence of thyroid,[43] thyroid hormones,[44] gonadotropin in males,[45] and testosterone and protein-rich diets [46] which, in normal animals, produce only renal hypertrophy and hyperfunction, causes a definite rise in the blood pressure of rats, with reduction of renal tissue and moderate hypertension.

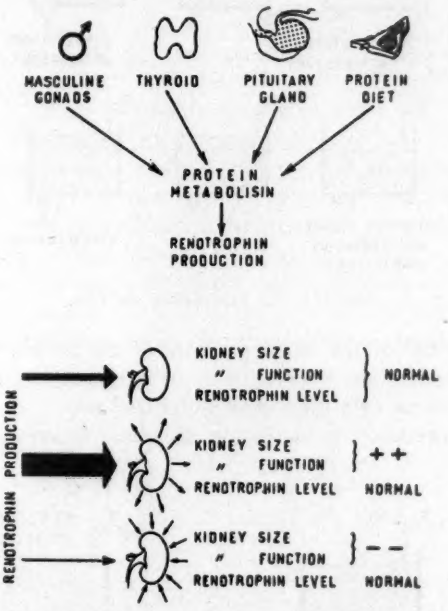

FIG. 11. The renotrophin hypothesis.

Again according to our hypothesis, the blood pressure of animals with renal experimental hypertension should be reduced or normalized if (1) the rate of renotrophin is reduced, or (2) the functional renal mass is increased (figure 14).

It has been shown that hypophysectomy [46, 50] and thyroidectomy,[44] and the administration of protein-poor diets,[51] which normally produce hypofunction and atrophy of the kidney, presumably because of decreased formation of renotrophin, cause in renal hypertensive rats a marked decrease in blood pressure.

To increase the renal mass we first recurred to parabiosis (figure 15).[52] Parabiotic union of a chronically hypertensive rat with a normal partner

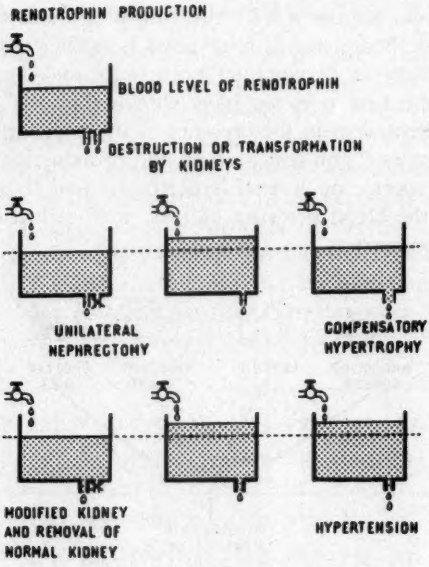

FIG. 12. For explanation see text.

is followed by a fall of the blood pressure of the former to normal levels. This does not occur if the hypertensive rat is united in parabiosis with another hypertensive rat or with a nephrectomized rat.

The ideal procedure for increasing the renal functional mass would be

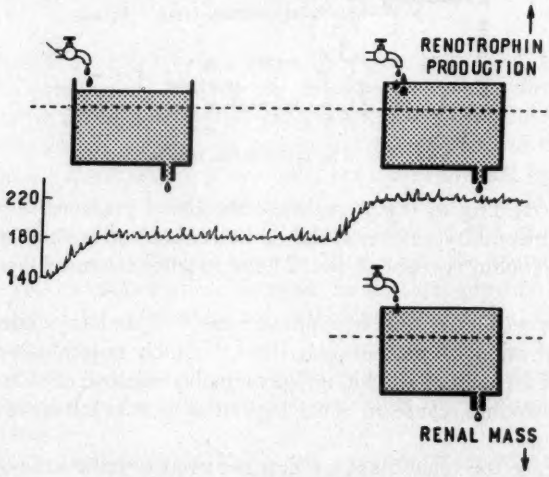

FIG. 13. For explanation see text.

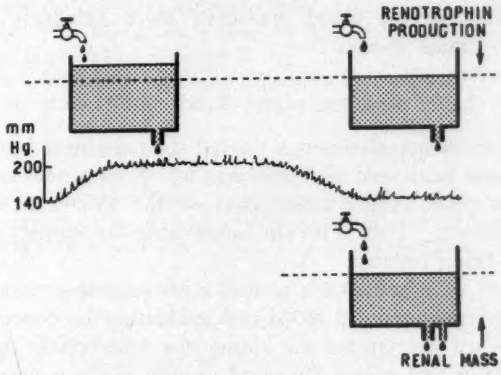

FIG. 14. For explanation see text.

the vascular transplant of a normal kidney. In animals the problem of renal transplant is not yet solved. Kolff [53] has observed a decrease of blood pressure in dogs with experimental hypertension following the vascular transplantation of a normal kidney, and recently Blaquier et al.[54] have reported similar results in rats. These are, however, acute experiments. The only experiments in which the transplant of a normal kidney to a hypertensive animal has been successful (survival of the transplant and long-last-

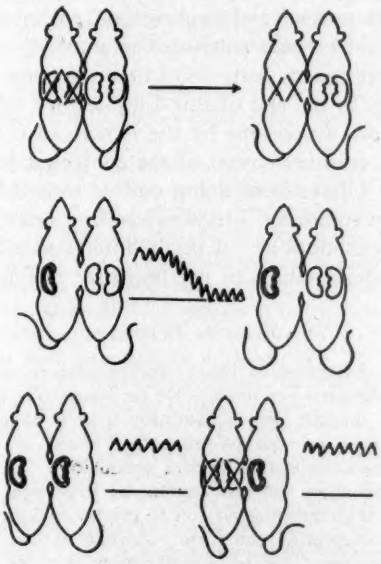

FIG. 15. For explanation see text.

ing normalization of the blood pressure) have, curiously enough, been realized in the human species.[55]

The Quest for Renotrophin

The renotrophin hypothesis has proved its soundness by its accordance with experimental facts, and its usefulness by opening new lines of inquiry.

Its weakest point is the assumption of the existence of a substance which is still elusive. This is no sin, since many substances were presumed to exist before being isolated.

Many efforts have been made to find a convenient method for detecting the presence of renotrophin in blood and evaluating its concentration. We presume that when we remove one kidney the renotrophin concentration in the blood increases and causes the rapid growth of the contralateral kidney, a phenomenon called compensatory hypertrophy. We presume that when we remove both kidneys the renotrophin in the blood increases rapidly. If we unite in parabiosis a nephrectomized rat with a normal animal, the kidneys of the latter increase rapidly in size and function.

But these methods for revealing the presence of renotrophin cannot be used for its detection and eventual isolation. In our quest for such a method we have followed many trails without success.

The methods we are now exploring are (1) the effect of repeated injections of plasma from nephrectomized animals on the number of mitoses in the kidney cortex of normal animals treated with colchicine, and (2) the effect of plasma from normal and nephrectomized animals on the survival and development of kidney cells cultivated in vitro.

The results of preliminary tests seem to show some promise of success.

I have the feeling, at the end of this Lilly lecture, of being unworthy of the great honor bestowed upon me by the American College of Physicians. Instead of giving an erudite account of the subject, I have simply told you of some experiments I have been doing and of some ideas I have in mind upon the subject. In summary, I have talked to you as I would have if you had been visiting my laboratory. I don't think I should excuse myself for this. At any rate, the briefness of my talk may facilitate your indulgence.

Summario in Interlingua

Le rolo del ren in hypertension renal experimental—e probabilemente etiam in hypertension renal in humanos—es duple. De un latere, iste organo exerce un forte action prohypertensive, mediate per le liberation a in le sanguine de un substantia pressori. Del altere latere, le histos del ren normal exerce un certe genere de effecto antihypertensive, le natura del qual es ancora speculative.

Le effecto prohypertensive del ren resulta del liberation de renina. Isto affice le globulina sanguinee angiotensinogeno con le resultante formation de angiotensina. E angiotensina es un octapeptido con forte activitate vasoconstrictori. Augmentate quantitates de renina ha essite trovate in le sanguine in casos de hypertension acute, tanto experimental como etiam in humanos. In casos de hypertension chronic, le

resultatos del investigationes ha remanite contradictori. Sed augmentate quantitates de angiotensina ha essite trovate in le sanguine de chronicamente hypertensive canes e de patientes con hypertension maligne.

Le action antihypertensive del ren es discutite ab le puncto de vista del hypothese a renotrophina. Secundo iste theoria, hypertension resulta quando le production de renotrophina excede le capacitate del ren de destruer, utilisar, o transformar lo. Il ha essite possibile monstrar que conditiones experimental que accelera le production de renotrophina o que reduce le massa functional del ren resulta in un augmento del pression sanguinee. Del altere latere, le pression sanguinee de animales con hypertension renal experimental es reducite o normalisate quando le intensitate del production de renotrophina es reducite o quando le massa functional del ren es augmentate.

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SERUM CHOLESTEROL, ELECTROPHORETIC LIPID PATTERN, DIET AND CORONARY ARTERY DISEASE: A STUDY IN CORONARY PATIENTS AND IN HEALTHY MEN OF DIFFERENT ORIGIN AND OCCUPATIONS IN ISRAEL *

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INTRODUCTION

IT is generally accepted today that there is a relationship between arteriosclerosis and disturbances in lipid metabolism. Morrison et al.,[1] and Steiner [2] have shown that patients with coronary disease as a group are characterized by hypercholesterolemia in comparison with control groups of healthy subjects of the same age.

In their survey of the incidence of coronary artery disease in various countries, Keys et al.[3] have shown that in those countries where hypercholesterolemia is frequently found after the age of 40 there is an increased incidence of cases of myocardial infarction anginal syndrome.

However, every investigation on these lines comes up against the same obstacle—the fact that there is a considerable overlap in the total cholesterol levels among the coronary patients and the control group. It thus seems logical to seek some other lipid or lipid-fraction which could serve as a clearer indicator of atherogenic activity.

Gertler et al.[4] and Oliver and Boyd [5] have shown that in coronary patients there is a rise in the ratio of total serum cholesterol to total serum phospholipid.

Cholesterol is carried in the serum in the form of lipoprotein complexes which can be investigated and split up into their component fractions by various chemical and physicochemical methods. Gofman et al.[6] used the ultracentrifuge. Russ et al.[7] used Cohn fractionation.

The third method is analysis by paper electrophoresis. This method, which is relatively simple and does not require expensive equipment, has been used by various investigators; the technic is not, however, completely standardized, and so the results have sometimes varied.[8, 9, 10]

In this paper we present a report of the electrophoretic examination of

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lipids among patients with myocardial infarction and among healthy subjects, divided into groups according to their occupation or ethnologic origin.

Conditions in Israel present an excellent opportunity for the investigation of the relationship between lipid patterns, dietary habits and incidence of coronary disease. The population is composed of "Ashkenazi" Jews who have immigrated from Europe, the United States and South Africa, and of "Sephardi" Jews who originate from the Mediterranean area and the Middle East. Among the "Sephardi" Jews one particular community is of especial interest—the Yemenites. Their number today in Israel is approximately 118,000. The Yemenite Jews have lived in Yemen in the Arabian Peninsula for some 2,000 years in comparative isolation. They have immigrated to Israel during the last 30 years.

In previous articles we have noted the great differences in morbidity and mortality due to arteriosclerotic heart disease among the various communities in Israel. The "Ashkenazi" Jews show the same high incidence seen in such Western countries as Great Britain and the United States, whereas there are almost no cases of coronary artery disease among the Yemenites.[11] It has been shown that Yemenite Jews who have immigrated recently have extremely low levels of total serum cholesterol and serum phospholipids. "Ashkenazi" Jews have lipid patterns similar to those common in Great Britain and the United States.[12]

Other investigations have confirmed the low levels of total cholesterol and other lipids among the Yemenites.[13]

Methods and Materials

The following groups were examined:

Group I comprised 74 male patients who had recovered from a myocardial infarction which was diagnosed clinically in each case, with electrocardiographic confirmation. The blood was examined when the patients were in a stable clinical condition at least 20 days after the onset of the attack. The age in this group was from 40 to 62 years; we fixed the upper age limit of 62 since it is possible that in cases of myocardial infarction occurring in elderly subjects other factors are involved which differ from those operating among younger patients. Similarly, we did not include patients suffering from severe congestive failure or diabetes mellitus. Apart from these exceptions, the group consisted of successive male cases of myocardial infarction who were admitted to our department.

Group II consisted of 32 Yemenite agricultural workers between 28 and 46 years of age, the average age being 37.5 years. They had all been living in a coöperative small-holders' village for nine years. None of them had any signs of heart disease or arteriosclerosis in general, and all of them were physically fit and capable of heavy manual work.

Group III consisted of 36 workers who were members of a well estab-

lished collective village ("Kibbutz") on the Coastal Plain. They were between 29 and 48 years of age, the average age being 41.2 years. The great majority of them were born in Central Europe and had immigrated some 20 years before. They were all healthy and capable of heavy manual work.

Group IV consisted of workers in the port of Jaffa who had been working for many years as porters and stevedores. In their general health and cultural background they were similar to the group of "Kibbutz" members. They were from 30 to 46 years of age, the average age being 39.8 years.

Group V consisted of 30 men, in good general health and working in various occupations, who were admitted to the hospital for minor surgical procedures such as hemorrhoidectomy or repair of hernia. They were between 30 and 55 years of age, the average age being 43.3 years. None of them showed signs of cardiac disease.

TABLE 1

Repartition of Subjects Under Investigation

Group		Number of Cases	Range of Age	Average Age
I	Coronary patients	74	40–62	53.4
II	Yemenite small holders	32	28–46	37.5
III	Agricultural worker of European origin living in a collective settlement (Kibbutz)	36	29–48	41.2
IV	Stevedores (European origin)	19	30–46	39.8
V	Healthy men of European origin, undergoing minor surgical procedures	30	30–55	43.3
VI	Physicians of Medical Staff of the Hospital	30	29–46	36.9

Group VI consisted of 30 doctors on the hospital staff. Their ages were from 29 to 46 years, the average age being 36.9 years. They were all apparently in good health. It is noteworthy that this group of doctors had a younger average age than any of the other groups. They were all of European origin.

We wish to emphasize that the choice of the various groups to be investigated was purely arbitrary. In fact, in some of the groups the subjects undergoing the investigation comprised every person who happened to be in that particular category. Thus, the doctors comprised nearly the whole medical staff of the hospital within the requisite age limits; similarly, the Yemenites and "Kibbutz" members comprised nearly all the male inhabitants of their villages within the age limits (table 1).

In every case the following investigations were performed: total cholesterol and total phospholipids with the cholesterol-phospholipid ratio; by paper electrophoresis, the distribution of cholesterol, phospholipid and total lipid between the alpha and beta globulin fractions of the serum. From these relative figures we calculated the absolute levels in milligrams per cent of alpha cholesterol and beta cholesterol, of alpha and beta phospholipid,

the alpha cholesterol : alpha phospholipid ratio and the beta cholesterol : beta phospholipid ratio.* The methods of chemical analysis were as follows:

Blood was taken from patients in a fasting state and tests were made within 24 hours in most cases. In the few cases where this was technically impossible, the blood was kept at 5° C. for not more than 48 hours.

The total serum cholesterol was estimated by the precipitation of proteins with alcohol ether, the lipids were taken up by chloroform, and the cholesterol was measured by the Buchardt-Liebermann reaction.[14, 15]

To eliminate serial errors, two separate estimations were carried out on two consecutive days.

Total phospholipids were estimated by determining the inorganic phosphorus bound to lipids and multiplying with a factor of 25. As in cholesterol estimation, proteins were precipitated by alcohol ether mixture, aliquots were taken and evaporated to dryness, organic matter was consumed by sulfuric acid, and the phosphorus was estimated with amino-naphthol-sulfonic acid.[16]

The lipid pattern of the blood serum was established by paper electrophoresis. A horizontal Grassmann-type camera was used. A buffer solution of ionic strength 0.05 pH 8.6 with a running time of six hours at 250 volts was utilized.

Six strips for each serum were run simultaneously; two strips were dyed with Sudan black for lipoprotein; two strips were washed three times with hot acetone for five minutes and then dyed with Sudan black for phospholipids; the remaining two strips were cut into three equal segments corresponding to the two lipid zones and one blank.

The dyed strips were evaluated by direct densitometry. Curves were plotted from optical density readings and the so designated areas were evaluated by planimetry. The segments from the last two strips were immersed in methanol chloroform for lipid extraction. After evaporation of the methanol chloroform, cholesterol was estimated by Slatzky's method. Each strip carried its own blank from the third segment.

To establish whether the chloroform methanol mixture eluted all the cholesterol from the strips, the following checks were made: A certain quantity of cholesterol in solution was placed on the paper strip in addition to the serum and was reclaimed from the strip with a deviation of ± 5%. To establish whether paper absorption could be a major source of error, we made the following tests:

Sera were applied to the paper and after the run was completed the current was reversed and a second run made. The paper was cut into segments and the cholesterol content of the strips was established. In this way we found that, provided the path of migration does not exceed 6 cm., absorption was well below 5% and therefore without major influence on the total contents of the cholesterol from the different fractions.

In this way we established two major lipoprotein fractions in the blood serum, the alpha and beta lipoprotein which contain the cholesterol as well as phospholipids bound to the proteins of the serum.

Results

Table 2 shows in each group the mean values (with standard deviation) for each lipid and for the ratios of the various fractions.

Very striking is the finding that there are considerable differences in the

* By alpha cholesterol we refer to the cholesterol carried in the albumin and alpha globulin, and by beta cholesterol that carried in the beta globulin and adsorption from the point of application. We make a similar use of the terms alpha and beta phospholipid.

lipid levels and ratios between the group of Yemenites and all the other groups, including the coronary patients. The other groups show no such great differences among themselves. The chief differences are in the levels of total serum cholesterol and in the beta cholesterol level.

TABLE 2

Mean Lipid Values and Lipid Ratio Values in the Different Investigated Groups

Group	Total Cholest. mg. per 100 ml. S.D.	Total Phospho-lipid mg. per 100 ml. S.D.	Cholest. Phospho-lipid Ratio S.D.	Percentage Alpha Cholest. S.D.	Alpha Cholest. mg. per 100 ml. S.D.	Beta Cholest. mg. per 100 ml. S.D.
I. Coronary Patients, 75 Cases	264 ± 43.1	308 ± 43.6	0.86 ± 0.10	14 ± 3.13	37 ± 6.05	222 ± 40.5
II. Yemenites, 32 Men	159 ± 19.6	213 ± 35.6	0.73 ± 0.10	27 ± 4.90	41 ± 6.20	121 ± 19.5
III. Members of Collective Settlement, 36 Men	199 ± 40.4	279 ± 38.8	0.73 ± 0.02	22.5 ± 5.84	44.7 ± 2.90	154 ± 40.0
IV. Stevedores, 19 Men	214 ± 25.8	293 ± 55.1	0.73 ± 0.13	20 ± 5.70	42.8 ± 3.70	171 ± 33.6
V. Healthy Ashkenazi, 30 Men (Minor Surgery)	220 ± 48.2	287 ± 49.4	0.76 ± 0.12	21.3 ± 7.20	46.8 ± 5.10	173 ± 45.3
VI. Physicians, 30 Men	236 ± 44.0	289 ± 49.6	0.82 ± 0.11	18.3 ± 5.70	43.2 ± 3.90	192 ± 41.5

Group	Percentage Alpha Phospho-lipid S.D.	Alpha Phospho-lipid mg. per 100 ml. S.D.	Beta Phospho-lipid mg. per 100 ml. S.D.	Alpha Chol. Alpha Phospho-lipid Ratio S.D.	Beta Chol. Beta Phospho-lipid Ratio S.D.	Percentage Alpha Lipo-protein S.D.
I. Coronary Patients, 75 Cases	43.7 ± 12.7	134 ± 29.2	173 ± 45.7	0.27 ± 0.10	1.33 ± 0.54	16.6 ± 3.50
II. Yemenites, 32 Men	52.0 ± 5.90	114 ± 15.9	107 ± 26.0	0.36 ± 0.05	1.16 ± 0.26	31.0 ± 6.60
III. Members of Collective Settlement, 36 Men	45.0 ± 6.30	125 ± 24.3	154 ± 34.2	0.36 ± 0.13	1.00 ± 0.33	23.0 ± 8.80
IV. Stevedores, 19 Men	40.7 ± 3.30	111 ± 30.2	182 ± 18.3	0.36 ± 0.09	1.07 ± 0.17	20.6 ± 7.30
V. Healthy Ashkenazi, 30 Men (Minor Surgery)	43.1 ± 9.20	125 ± 25.8	161 ± 47.0	0.37 ± 0.03	1.07 ± 0.24	21.2 ± 8.20
VI. Physicians, 30 Men	41.5 ± 8.20	118 ± 28.8	171 ± 34.8	0.37 ± 0.07	1.12 ± 0.06	18.8 ± 4.80

TOTAL CHOLESTEROL AND BETA CHOLESTEROL IN CORONARY ARTERY DISEASE

In figure 1 each column represents the total serum cholesterol for a coronary patient, and the shaded area shows the level of beta cholesterol in each case. There is much discussion at present in the literature as to what is the upper level of the normal serum cholesterol. In view of the latest

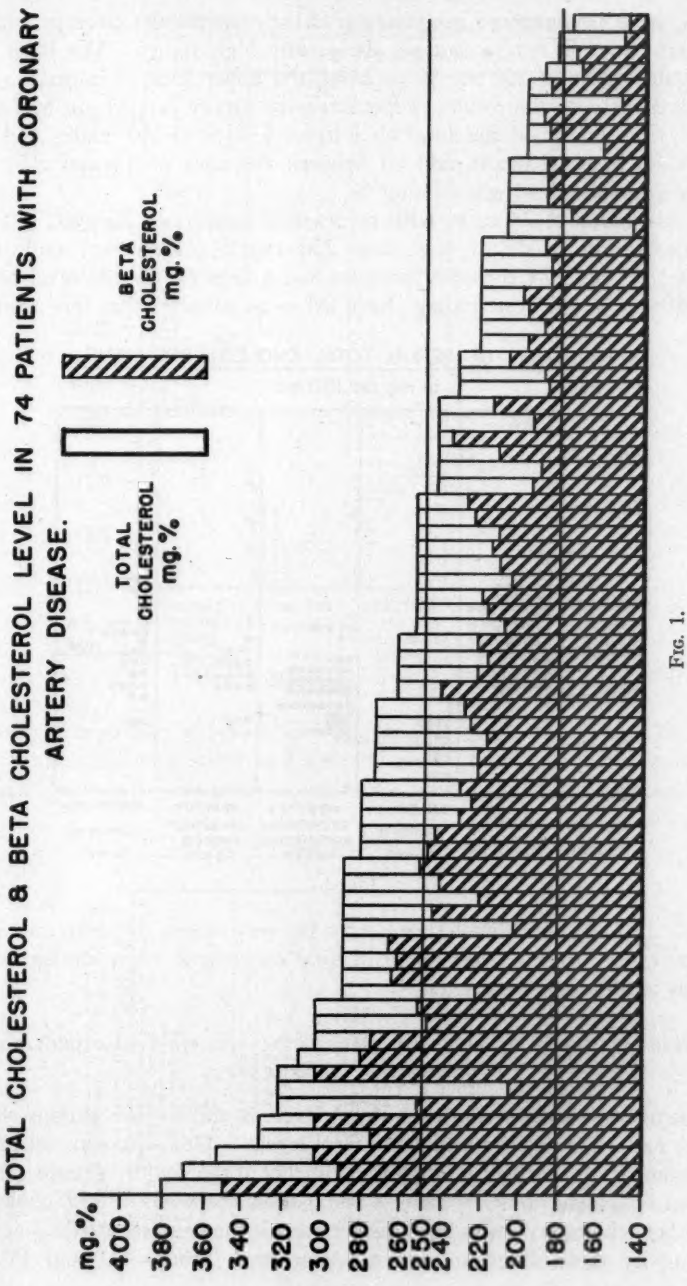
TOTAL CHOLESTEROL & BETA CHOLESTEROL LEVEL IN 74 PATIENTS WITH CORONARY ARTERY DISEASE.
TOTAL CHOLESTEROL mg.%
BETA CHOLESTEROL mg.%
mg.%
400
380
360
340
320
300
280
260
250
240
220
200
180
160
140

FIG. 1.

reports, it is pertinent to ask whether what we call the average normal cholesterol level is not in fact an abnormally high figure. We have considered the figure of 250 mg.% as being the upper level of normal. This figure accords with the results of the extensive survey carried out by Lawry et al.,[17] who examined the total cholesterol level in 1,501 males and 412 females, all in good health and all between the ages of 45 and 59. The average figure obtained was 245 mg.%.

In our group of 74 cases with myocardial infarction, 30 (40.7%) had total cholesterol levels of less than 250 mg.%. However, only eight (10.8%) of these 74 coronary patients had a beta cholesterol level of less than 180 mg.%. These findings have led us to consider that this arbitrary

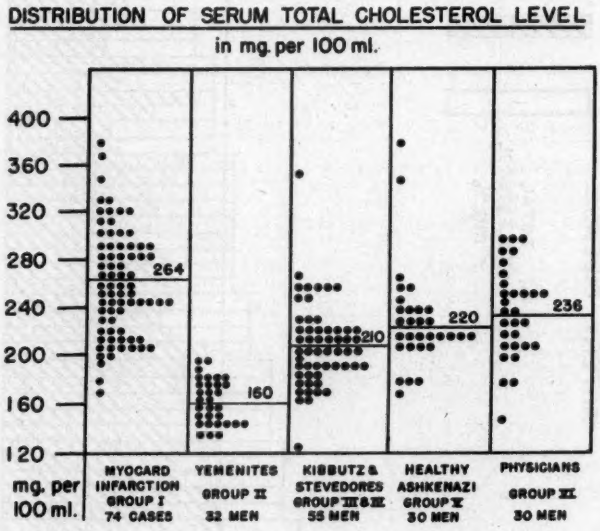

FIG. 2.

level of 180 mg. beta cholesterol may be very useful in overcoming the obstacle caused by the overlapping of total cholesterol levels among healthy subjects and coronary patients.

LIPID PATTERNS OF HEALTHY MALES ACCORDING TO ETHNOLOGIC ORIGIN AND OCCUPATIONS

The average total serum cholesterol levels in the various groups show a definite pattern, as do the beta cholesterol levels. This is of especial interest when comparing the levels among the subjects in the healthy groups (figures 2, 3 and 4). Diagrams in figures 2 and 3 show the levels of total cholesterol and of beta cholesterol in milligrams per cent in the form of scatter diagrams. To simplify these diagrams, we have included Groups III and IV (the

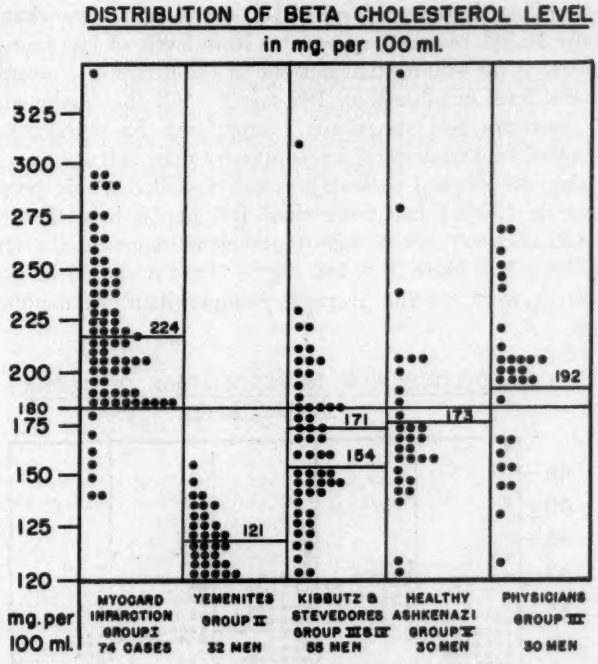

FIG. 3.

stevedores and the "Kibbutz" members) as a single unit, since they have very similar lipid patterns and resemble each other very closely in their social backgrounds and occupations. We have noted previously that if we

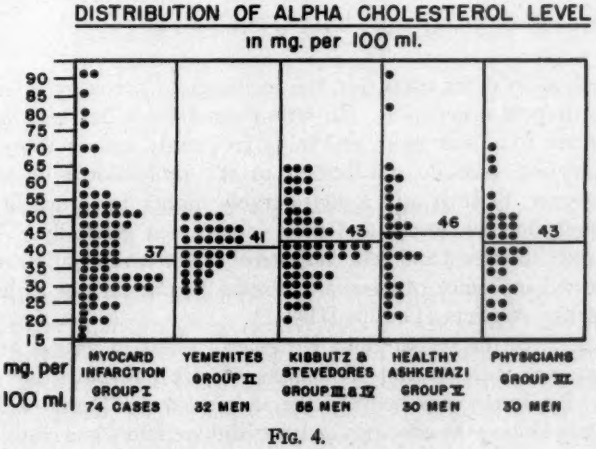

FIG. 4.

take the serum beta cholesterol level of 180 mg.% as a somewhat arbitrary standard, only 10.8% of coronary patients have levels of less than this. Of especial interest is the finding that not one of the group of Yemenites had a beta cholesterol level of *more* than 180 mg.%. Of the combined group of "Kibbutz" members and stevedores (comprising 55 subjects), only 14 (25.4%) showed beta cholesterol levels of *more* than 180 mg.%. In Group V (comprising 30 surgical patients), which included a fair proportion of clerks, etc., nine (30%) had more than 180 mg.% beta cholesterol. In Group VI (30 doctors), which may be taken to represent the free professions, 21 (70%) had more than 180 mg.%; here it should be noted again that the doctors were, on the average, younger than the members of the other groups.

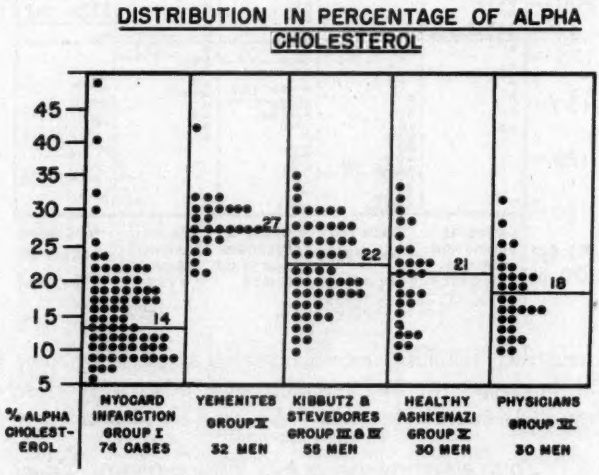

FIG. 5.

In Israel, as in other countries, the incidence of coronary artery disease varies according to occupation. In recent years there has been a tendency for this disease to appear more and more frequently among those members of the population who do not belong to the professional or managerial classes; however, there is still a considerably higher incidence of coronary disease among doctors, clerks and professional men generally. The levels of total serum cholesterol and beta cholesterol in our investigation correspond to the expected incidence of coronary disease in the various groups of apparently healthy subjects (Groups III–VI).

Comparison of the serum alpha cholesterol levels in all the groups (including coronary patients and Yemenites—figure 4) shows no significant differences; the levels vary between the rather narrow limits of 20 and 65 mg.%. Only among the coronary patients did we find some cases with over

65 mg.% alpha cholesterol, but this was due to the very high total cholesterol levels in these cases.

We believe that there is especial importance in the considerable differences in the percentages of alpha cholesterol (figure 5). Although the Yemenites show the lowest absolute values for total serum cholesterol, they have the highest percentage of alpha cholesterol.

TABLE 3

Statistical Evaluation of Results *

	Total Cholest. mg. %	Beta Cholest. mg. %	Alpha Cholest. mg. %	Alpha Cholest. %	Cholest. Phospho-lipid Ratio
I. Coronary patients V. Surgical patients	Absolutely significant on more than 1% level	Absolutely significant on more than 1% level	Non significant	Probably significant on 5% level	Absolutely significant on more than 1% level
I. Coronary patients III. Kibbutz members	Absolutely significant on more than 1% level	Absolutely significant on more than 1% level	Non significant	Absolutely significant on more than 1% level	Absolutely significant on more than 1% level
I. Coronary patients VI. Physicians	Probably significant on 5% level	Non significant	Non significant	Non significant	Non significant
V. Surgical patients III. Kibbutz members	Non significant	Non significant	Non significant	Non significant	Non significant
V. Surgical patients VI. Physicians	Non significant	Non significant	Non significant	Non significant	Non significant
VI. Physicians III. Kibbutz members	Absolutely significant on more than 1% level	Absolutely significant on more than 1% level	Non significant	Absolutely significant on more than 1% level	Absolutely significant on more than 1% level
II. Yemenites III. Kibbutz members	Absolutely significant on more than 1% level	Absolutely significant on more than 1% level	Non significant	Absolutely significant on more than 1% level	Absolutely significant on more than 1% level

* Significance tests were carried out on the following formula: $tij = \frac{n_i - n_j}{\sqrt{\frac{\sigma_i^2}{n_i} + \frac{\sigma_j^2}{n_j}}}$.

The Yemenites have an average of 27% alpha cholesterol, while the group of coronary patients shows an average of 14% alpha cholesterol; thus among the Yemenites the percentage of alpha cholesterol is nearly double that of the coronary patients. The average value for the group of doctors comes next to that of the coronary patients, being 18.3% alpha cholesterol. The other groups of European origin (Groups III, IV and V) have values

in between those of the Yemenites and the doctors. From investigations in our laboratory, we have been able to show that the percentages of the alpha and beta fractions of cholesterol form a very stable element in the general lipid pattern; for example, in cases of hypercholesterolemia, where we have succeeded in reducing the total cholesterol level by means of slimming diets or giving unsaturated fast, the proportion of alpha to beta cholesterol has remained rather stable.

Statistical Analysis (Table 3)

From table 2 it can be seen that there are considerable differences in the total serum cholesterol levels and in the beta cholesterol levels in absolute figures as well as in the percentages of alpha cholesterol. There are only very small differences in the total phospholipid values and in the alpha or beta phospholipid fractions; the considerable variations in the cholesterol phospholipid ratios are accounted for by the variations of the total serum cholesterol. We have limited ourselves to a statistical analysis of these fractions. It is seen that there are no significant differences in the alpha cholesterol levels (i.e., absolute values in milligrams per cent) among the various groups investigated. However, between the group of coronary patients and the healthy groups, there are statistically significant differences in (a) the total serum cholesterol levels; (b) the beta cholesterol levels (absolute values in milligrams per cent); (c) the alpha cholesterol percentage;* (d) the total serum cholesterol-total phospholipid ratio.

It is seen that Group V, the "healthy" men undergoing minor surgical procedures, occupies the middle position between Group VI (the doctors) and Groups III and IV (the stevedores and "Kibbutz" members). We have previously noted that this group is composed of clerks, bookkeepers, etc., as well as manual workers.

An interesting picture is seen if we exclude the Yemenites and compare the various healthy groups of European origin. We find that there are no statistically significant differences on comparing Group V (the "surgical" patients) with any of the other healthy groups (Groups III, IV or VI). However, on comparing Group VI (the doctors), who have among the healthy groups the highest mean lipid levels, with Group III (the "Kibbutz" members with the lowest mean lipid levels), we find statistically significant differences (over the level of 1%) in the total cholesterol levels, in the beta cholesterol level, in the percentage of alpha cholesterol, and in the total cholesterol-total phospholipid ratio. It is noteworthy that if we compare Group I (the coronary patients) with Group VI (the doctors), we find no differences of statistical significance except for the total cholesterol level, which has only a probable statistical significance (on the 5% level). Com-

* In this survey we have found it convenient to make our comparisons in terms of percentages of alpha cholesterol; it is obvious that we could equally well have used the percentage of beta cholesterol which, of course, is in inverse proportion to the alpha cholesterol percentage.

paring the Yemenites (Group II) with the European group having the lowest mean lipid levels (i.e., the "Kibbutz" members, Group III), we find differences of absolute statistical significance (over the 1% level) for all the lipid fractions except for alpha cholesterol level in milligrams per cent.

A Survey of the Dietary Habits of a Group of Yemenite Jews *

Recently we have carried out a survey on an individual basis of the eating habits of Yemenite Jewish smallholders in a coöperative village. The subjects all came to Israel nine years ago and since then have lived in a smallholders' village based on coöperative principles. Their economic position is satisfactory. As subjects for investigation we chose 25 males between 30 and 50 years, all of them engaged in agricultural work, chiefly on their own smallholdings, and occasionally working for hire on other farms. To facilitate the investigation, the work on the spot was done by Yemenite district nurses who had been brought up and educated in Israel. These nurses actually lived in the village during the period of investigation, and they followed up every subject for one week. They visited the kitchens and weighed and measured the food. The detailed results of this survey, including the amounts of vitamins and minerals, will be published.[18]

Table 4

The Dietetic Composition and Some Biological Values from a Nutritional Survey in Yemenites (25 Males in a Cooperative Village)

Fat	55 gm. =	495 Cal. (22%)
Proteins	81 gm. =	324 Cal. (15%)
Carbohydrates	351 gm. =	1,404 Cal. (63%)
Total calories		2,223 Cal.
Average weight		58.5 kg.
Average height		167 cm.
Average hemoglobin concentration		12.6 gm. %
Average serum total protein		6.8 gm. %
Average albumin		4.2 gm. %

From table 4 it can be seen that the average food intake of a Yemenite agricultural worker per diem is 2,223 calories, of which only 495 calories (22%) were derived from fats. The average quantity of fat consumed was 55 gm. a day. Fifteen per cent of the calories was derived from proteins, and 63% from carbohydrates. It is worth noting that 62% of the total calories (1,376 calories) came from bread, which means that 71% of the protein and 81% of the carbohydrates were derived from bread only.

These figures, which are well below the averages for Western Europe and the United States, are likewise much lower than the average figures for Israel.

The diet of the Yemenites is noteworthy for its lack of diversity and for the fact that very little cooking is done. They do not drink milk or eat

* This survey was carried out in coöperation with Miss Kornfeld, head of the Dietetic Department of the "Malben" Organization in Israel.

cheese, and they appear to be unaware of the habit of spreading butter or margarine, etc., on bread. On the average, they eat meat once a week; they do not eat sausage. They eat vegetables chiefly in soup, but they also eat lots of fresh vegetables without any preparation. They are very fond of spices and condiments in various forms.

It should be noted that the men investigated were all accustomed to heavy manual work.

The investigation showed that the subjects investigated had an average height of 167 cm. and an average body weight of 58 kg. The "ideal" weight for a male 167 cm. tall, as calculated by American insurance companies,[19] is 64 kg.; thus the average weight of the Yemenites is 6 kg. less than the "ideal" weight. Of course, one may have grave doubts as to whether one can describe the average weights deducted from insurance statistics in the United States as being "ideal," especially in view of the problem facing us at the moment—the incidence of arteriosclerotic heart disease.

The average hemoglobin of these Yemenites was 12.6 gm.%, which is less than the average hemoglobin level of healthy men in the United States and the United Kingdom, and is even a little under the average for Israel. However, the total serum proteins and the albumin level, as well as the electrophoretic pattern of the protein fractions, were well within normal limits. On the other hand, the lipid patterns, as noted previously, were completely different from the average values for the rest of the population in Israel and for the population of European countries generally.

Discussion

There appear to be great advantages in making use of the beta cholesterol level instead of the total serum cholesterol level as an index of atherogenic activity. The extensive investigations carried out by the Technical Groups of the Committee on Lipoproteins and Atherosclerosis in four large centers over a period of several years led to conflicting results.[20] Gofman and his co-workers of the Donner Laboratory introduced the Atherogenic Index, based on a complicated formula of the "Lipoprotein Classes," which are differentiated by flotation in the ultracentrifuge; they claimed that the Atherogenic Index is more significant than the total serum cholesterol level as an indicator of atherogenic activity. However, the other investigators found that measuring the ultracentrifugal lipoprotein classes has no advantages over the simple determination of the total serum cholesterol as a means of identifying individuals with a tendency to myocardial infarction. They justify their attitude by the considerable overlapping that exists not only in the serum cholesterol but also in the various ultracentrifugal lipoprotein classes among coronary patients and healthy subjects. This prevents using these methods for predicting the development of atherosclerosis in individual subjects.

We attach great importance to the fact that, in our group of coronary

patients, only 10.8% had serum beta cholesterol levels of less than 180 mg.%, while 40.7% had total serum cholesterol levels within normal limits or below 250 mg.%. This figure is very close to the average level for healthy males between the ages of 49 and 59 as established by the Boston investigators. Thus, the serum beta cholesterol level appears to be superior as an indicator of atherogenic activity to all other lipids or lipid pattern combinations. This hypothesis is further supported by the fact that in a group of healthy subjects unaffected by arteriosclerosis, such as the Yemenites, we did not find a single subject having a serum beta cholesterol of over 180 mg.%. It should be remembered that all investigations of this type carried out in Western countries have to contend with the same drawback—that the "healthy" controls presumably suffer from atherosclerosis to some extent, either not severely, or else in a location which will not cause clinical manifestations. This may well be the explanation for the difficulty in finding significant differences in lipid levels. This drawback does not exist when the Yemenites are used as a control group of "healthy" subjects.

This investigation does not allow us to predict that every male with a beta cholesterol level of over 180 mg.% will become a victim of myocardial infarction, but it is possible to say that a male with less than 180 mg.% beta cholesterol has little chance of getting coronary artery disease.

This disparity between the total serum cholesterol level and the beta cholesterol level arises from the unequal distribution of cholesterol among the alpha and beta fractions in the serum lipoproteins. A simple calculation will show that a coronary patient with a total serum cholesterol of 210 mg.%, of which only 10% is carried in the alpha fraction, will have a beta cholesterol level of 189 mg.%. On the other hand, a healthy man having a serum total cholesterol level as high as 250 mg.%, of which 30% is carried in the alpha fraction, will show a beta cholesterol level of 175 mg.%.

This distribution of cholesterol between the alpha and beta lipoproteins is very stable. The low percentage of alpha cholesterol which characterizes the group of coronary patients is a typical feature of the process of coronary atherosclerosis, and appears also in those coronary patients whose total serum cholesterol is not raised. Table 5 shows that, in the group of coronary patients, the low percentage of alpha cholesterol is always near the region of 14%, not rising with the absolute level of the total serum cholesterol. On the other hand, the Yemenite group, despite their low total cholesterol level, have a high percentage of alpha cholesterol. This value is double the corresponding level in the coronary patients, and is 25% more than the corresponding level in the nearest group of European origin (i.e., Group III, "Kibbutz" members). In this respect, too, the group of doctors (Group VI) came closest to the group of coronary patients.

It is generally accepted that the total serum cholesterol level in healthy males rises with age from 20 to 55. Possibly this is a normal biologic process, but it may be, as we think, a result of the way of life, diet and

occupation customary among adult males in the Western world. We suggest, as a possible explanation, that males with the basic pattern of a low alpha cholesterol percentage, will reach, with the passage of the years, a higher total cholesterol level and so acquire a beta cholesterol level of over 180 mg.%, which is regarded as an index of excessive atherogenic activity.

The dietary survey which we carried out among the Yemenite smallholders shows a surprisingly low caloric level. The level is much below the average for the United Kingdom or the United States, and is even well

TABLE 5

Percentage of Alpha Cholesterol in 74 Coronary Patients

Total Cholesterol Level	Number of Cases	Mean Percentage of Alpha Cholesterol
160 mg. %–225 mg. %	21	13.5%
225 mg. %–250 mg. %	15	15.5%
250 mg. %–400 mg. %	58	14.5%

below the average for Israel. The difference is striking not only in the number of calories but also in the quantity of fats and in the percentage of calories derived from fats. Notwithstanding their poor diet, the Yemenites are fully capable of the hardest manual work.

It may be that, in addition to nutritional factors, the lipid pattern is influenced by the energy output. This assumption may help to explain the differences in the lipid patterns between the group of doctors and the groups of stevedores and the "Kibbutz" members. In Israel, members of the

TABLE 6

Comparisons of Lipid Pattern and Dietary Habits Among Bantus in South Africa and Yemenites in Israel

	Total Cholesterol	% Alpha Cholesterol	Beta Cholesterol mg. %	Gm. Fat per diem	Diet Fats % Cal.
Yemenites	159 ± 19.6	27% ± 4.9	121 ± 19.5	55	22%
Bantus (21)	166 ± 47.2	28.1%	122 ± 47.9	45	17%

Ashkenazi community (of European origin) of all classes have similar standards of living and dietary habits. The group of "Kibbutz" members, stevedores and doctors are all Ashkenazi Jews. The stevedores are well paid and they probably spend more on food than do the young doctors on the hospital staff. Thus it seems very likely that the energy output, which varies so much between manual workers and members of the free profession, is the decisive factor in determining lipid patterns and so possibly the incidence of coronary artery disease.

Our findings with the Yemenites approximate very closely the findings of Bronte-Stewart et al.[21] in their investigations of Bantus (table 6). Recently Page et al.,[22] from their investigations on American Indians and from animal experiments, have again put forward the hypothesis that there

is a strong racial and hereditary factor in the tendency to atherosclerosis.[23] *

Bantus and Yemenite Jews are utterly different in their culture, way of life and religion. They resemble each other in their lipid pattern, in their low proportion of fat, in their diet and in their immunity to coronary artery disease. Unlike the Bantus in South Africa, the Yemenites live as equals among the general population, and members of their community hold important positions in public life.

The fact that two racial groups as different as the Bantus and the Yemenite Jews appear to be immune to coronary artery disease goes against the supposition that the lipid patterns and the predisposition to coronary disease are due to factors of race or heredity, and tends to support the hypothesis that they are due to environmental causes, which we hope it will be possible to elucidate and control in the not too distant future.

Summary

1. Owing to the presence of Eastern and Western Jewish communities with very different incidences of arteriosclerotic heart diseases, Israel provides an excellent field for the investigation of the problem of arteriosclerosis.

2. An investigation has been carried out to determine, by analytic and paper electrophoretic methods, the lipid patterns of a group of coronary patients, of various groups of apparently healthy European Jews in different occupations, and of a group of Yemenite Jews.

3. It is suggested that the serum beta cholesterol levels in milligrams per cent are a better index of atherogenic activity than is the total serum cholesterol level or any other lipid or lipid pattern combination. Of 74 coronary patients, 40% had normal levels of total cholesterol (the normal upper level being taken as 250 mg.%), but only 10.8% had beta cholesterol levels of less than *180* mg.%. The group of Yemenite Jews examined did not show a single example with more than 180 mg.% beta cholesterol. The Yemenite Jews were free of evidence of coronary disease.

4. Among Jews of European origin divided into groups according to occupation, it was found that professional workers (physicians) had significantly higher average beta cholesterol levels than did manual workers.

5. A survey was carried out to determine the dietary habits of Yemenite smallholders.

6. The group of coronary patients showed a consistently low percentage of alpha cholesterol, which was independent of the total cholesterol level and/or the beta cholesterol level in milligrams per cent.

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* In a previous communication we noted that Yemenites who have been more than 25 years in Israel and have assimilated the European way of life have lipid patterns more nearly similar to those of the European Jews.[12]

We wish also to thank Dr. G. Kallner, Chief of the Statistical Department of the Israel Government, and Mrs. Ora Engelberg for supplying statistical analyses.

SUMMARIO IN INTERLINGUA

In consequentia del extense immigration in Israel in recente annos, le population de ille pais es un composito de judeos europee, i.e. de "ashkenazim," e de judeos ab le areas del Mediterraneo e del Oriente medie, i.e. de "sephardim." Le ashkenazim ha le mesme alte morbiditate e mortalitate ab atherosclerotic morbo cardiac como le population del paises occidental. Le sephardim, del altere latere, ha un basse incidentia de ischemic morbo cardiac, sed illes include un gruppo ethnic particular, le judeos yemenita, qui—a etates medie—ha nulle morbo de arteria coronari del toto.

Le presente articulo reporta le resultatos de analyses chimic e de studios per electrophorese a papiro in re le lipidos seral in le supra-mentionate gruppos del population de Israel. In le studios electrophoretic le lipoproteinas alpha e le lipoproteinas beta esseva eluite ab le papiro post lor migration, e le cholesteroles alpha e beta esseva determinate.

Le resultatos prova que si on studia e compara nivellos de cholesterol beta in loco del nivellos de cholesterol total in le sero, on trova un reduction considerabile del area de coincidentia inter le valores pro patientes coronari e le valores pro normal subjectos de controlo.

Inter 74 patientes coronari de etates de inter 40 e 62 annos, 40% habeva nivellos de cholesterol total de infra 20 mg per 100 ml de sero. Solmente 10,8% del mesme gruppo habeva nivellos de cholesterol beta de infra 180 mg per 100 ml de sero.

Inter 32 agricultores yemenita, nulle caso esseva incontrate in que le nivello de cholesterol beta excedeva 180 mg per 100 ml de sero.

Inter 55 obreros maritime e agricultural de origine europeo-ashkenazi, 25,4% habeva nivellos de cholesterol beta de plus que 180 mg per 100 ml. In un gruppo de ashkenazim in varie professiones manual e non-manual, 30% habeva nivellos de cholesterol beta de plus que 180 mg per 100 ml. Per contrasto con iste cifras, in un gruppo de 30 medicos del personal del Hospital Governamental Donolo a Jaffa, 70% habeva nivellos de cholesterol beta de plus que 180 mg per 100 ml. (Le extremos de etate in omne le gruppos de normales esseva 28 e 55 annos. Le etates medie intra le varie gruppos esseva inter 37,5 e 43,3 annos.)

Le differentia inter le nivellos de cholesterol total e le nivellos de cholesterol beta in le patientes coronari se explica per le facto que solmente un micre procentage del cholesterol es connectite con le lipoproteinas alpha. Le valor medie pro cholesterol alpha esseva 14% ± 3,13. Iste basse procentage esseva constante, sin reguardo a si le nivello de cholesterol total in patientes con morbo coronari esseva alte (inter 250 e 400 mg per 100 ml), normal (inter 200 e 250 mg per 100 ml), o basse (infra 200 mg per 100 ml).

Del altere latere, le procentage de cholesterol alpha inter le judeos yemenita esseva 27% ± 4,9, i.e. approximativemente duo vices le procentage trovate in le gruppos coronari.

Le procentages medie de cholesterol alpha in le altere gruppos normal esseva 20% ± 5,7 (obreros maritime), 21,3% ± 7,2 (gruppo mixte de ashkenazim, e 18,3% ± 5,7 (medicos).

Il existe un correlation distincte inter le nivello absolute de cholesterol beta e le procentage de cholesterol alpha e le incidentia de morbo coronari in le varie gruppos normal. Il etiam existe un statisticamente significative differentia ($p < 0,01$) quanto al nivellos e proportiones lipidic inter le patientes coronari e le normales europeo-ashkenazi (excepte le medicos) e inter le gruppo de ashkenazim con le plus basse nivellos lipidic, i.e. le obreros maritime, e le judeos yemenita.

In un studio nutritional de 25 agricultores yemenita in que cata un del subjectos esseva observate durante octo dies, il esseva trovate que le diurne ingestion medie de alimentos amontava a 2.223 calorias. Le ingestion diurne de grassia amontava a 55 g, representante 22% del calorias. Le ingestion diurne de proteinas amontava a 81 g, representante 15% del calorias. Le ingestion diurne de hydratos de carbon amontava a 351 g, representante 63% del calorias.

Le peso corporee medie del yemenitas examinate esseva 6,1 kg infra le valor ideal. Le valores pro hemoglobina e le proteinas del sero esseva intra le limites del norma pro le region. Solmente le nivellos lipidic esseva multo basse.

Il es probabile que le difficultates notate per autores american in distinguer le configurationes lipidic de patientes coronari ab illos de normal subjectos de controlo resulta del facto que le subjectos de controlo usate in America es individuos con un certe grado de activitate atherogene, ben que sin symptomas clinic. Iste problema pote esser resolvite solmente si le subjectos de controlo usate es individuos qui, como le yemenitas, es libere de omne atheromatosis coronari.

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THE NEPHROTIC SYNDROME IN ADULTS: A COMMON DISORDER WITH MANY CAUSES *

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The metabolic, nutritional and clinical consequences of continued massive albuminuria constitute the nephrotic syndrome. Florid cases are readily recognized from infancy [1, 2] to extreme old age,[3] and the diagnosis can be confirmed rapidly in the laboratory by urinalysis and simple biochemical studies of the blood. The nephrotic syndrome was first described by Richard Bright,[4] who noted the association of proteinuria, hypoproteinemia and lipemia with edema of renal origin, and it has long been recognized as one manifestation of glomerulonephritis. From our experience with 98 adult patients studied by renal biopsy it is apparent that the syndrome may be due to a variety of causes and different pathologic changes in the kidney (table 4). Nevertheless, it is still considered by some to be a single disease entity.[5] The confusion which still exists about the different etiologies of the nephrotic syndrome has been caused by semantic difficulties, by the lack of correlation between pathologic findings and clinical data, by the disharmonious views of pediatricians and internists about the natural history of the syndrome, and by our imperfect knowledge of the mechanisms which produce its metabolic and clinical manifestations.

Metabolic and Nutritional Consequences of Continued Massive Proteinuria

The well known metabolic hallmarks of the nephrotic syndrome are proteinuria, hypoalbuminemia and hypercholesterolemia. But the full-blown picture presents many more biochemical aberrations than this. Albumin is the major protein lost in the urine, accounting for approximately 70% of the total. As can be seen from table 1, other plasma proteins, such as ceruloplasmin, also run to waste in the urine. The continued drain of nitrogen in the urine also compromises the tissue and cellular stores of protein, and

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the clinical consequences of this impoverishment are tissue wastage, malnutrition, fatty metamorphosis of the liver, sodium retention, hydremia and edema. Depletion of complement makes the nephrotic patient particularly susceptible to infection, and loss of specialized proteins, such as those which bind thyroid hormone and iron, explains satisfactorily the apparent hypo-

TABLE 1

Some Biochemical Changes in the Urine of Patients with the Nephrotic Syndrome

Increased	Decreased	Variable
Albumin [6, 7]	Sodium chloride	Glucose [6]
$Alpha_1$ globulin [6, 7]		Potassium
$Alpha_2$ globulin [6, 7]		Amino acids [6]
Beta globulin [6, 7]		Nitrogen
Gamma globulin [6, 7]		
Protein-bound iodine [8, 9]		
Ceruloplasmin [10]		
Siderophilin [10, 11]		
Antidiuretic substance [12]		
Complement [13]		
Prothrombin [14]		
Antithrombin [14]		
Proconvertin [14]		

thyroidism and tendency to anemia. More difficult to explain is the marked increase in circulating serum lipids and relatively large plasma proteins, such as cholinesterase and fibrinogen (table 2).

These changes may develop as a result of disturbances in the transport of fats,[18] or they may be the result of some as yet unidentified mechanism. We have speculated elsewhere [19] that the metabolic changes seen in the nephrotic syndrome are the result of increased hepatic synthesis of proteins

TABLE 2

Some Biochemical Changes in the Blood of Patients with the Nephrotic Syndrome

Increased	Decreased	Variable
Total lipid [4]	Albumin	$Alpha_1$ globulin [6]
Triglycerides	Protein-bound iodine [9]	Gamma globulin [6]
Phospholipids	Siderophilin [10, 11]	Alpha lipoprotein [6]
Free cholesterol	Ceruloplasmin [10]	Sodium
Cholesterol esters	Complement [16]	Chloride
Beta lipoprotein [6]	Osmotic pressure [17]	Calcium
$Alpha_2$ globulin [6]	Plasma volume [6]	
Beta globulin [6]		
Fibrinogen [6]		
Cholinesterase [15]		

and fats, called forth by depletion of hepatic albumin and made evident by the retention of large molecular protein molecules in the blood stream and the loss of the small ones in the urine. Be this as it may, studies on nephrotic rats [20] and man [19, 21] have clearly demonstrated that infusion of large amounts of serum albumin can restore both the protein and the lipid abnormalities in the plasma to normal.

Massive loss of albumin in the urine is not invariably accompanied by

TABLE 3

Causes of the Nephrotic Syndrome

	Reference Number
1. *Heredofamilial*	(1)
2. *Infective*	
Syphilis	(22)
Malaria	(25, 26)
Subacute bacterial endocarditis	(27)
Tuberculosis*	(23)
Diphtheria*	(24)
3. *Toxins*	
Organic mercurials*	(33, 34)
Inorganic mercurials (teething powders)	(35)
Tridione, Paradione*	(40, 41, 42)
Bismuth*	(36)
Gold*	(37, 38, 39)
Trichlorethylene*	(52)
4. *Allergic*	
Poison oak*	(29)
Bee sting*	(31, 32)
Pollens and dust	(28)
Serum sickness	(30)
5. *Mechanical*	
Renal vein thrombosis	(43, 44, 45)
Constrictive pericarditis	(45)
Congestive cardiac failure	(46)
Tricuspid valve disease	(47)
Thrombosis or obstruction of inferior vena cava	(48)
6. *Generalized Disease Processes*	
Amyloidosis—primary	(51)
Amyloidosis—secondary	(4)
Myelomatosis	(49)
Systemic lupus erythematosus	(53)
Diabetic glomerulosclerosis	(55, 56)
Schönlein-Henoch purpura	(50)
Arteriolar nephrosclerosis	(62)
Progressive systemic sclerosis*	(52)
Polyarteritis nodosa*	(52)
Sickle cell anemia*	(52)
7. *Intrinsic Renal Disease*	
Membranous glomerulonephritis	(3)
Proliferative glomerulonephritis	(67)
Mixed membranous and proliferative glomerulonephritis	(61)
Tubular degeneration; no glomerular lesions (lipoid nephrosis)	(66)
Tubular degeneration; minimal glomerular lesions	(66)

* These causes have not been thoroughly validated.

all of the clinical or biochemical stigmata of the nephrotic syndrome. The loss of protein may not be sufficient to overwhelm the body's homeostatic mechanisms, and clinical edema may never appear. These patients with subclinical forms feel well, and rarely appear in the clinic unless proteinuria is detected on routine examination. In other *formes frustes* the serum lipid levels are normal or decreased in amount. The reasons for this are not clear. In our experience low or normal levels of serum cholesterol may

accompany the nephrotic syndrome in generalized disease processes, e.g., systemic lupus erythematosus, and may well indicate a poor prognosis.

The Causes of the Nephrotic Syndrome

The many conditions reported to have been associated with the nephrotic syndrome are summarized in table 3. It is immediately evident that the nephrotic syndrome is not a single disease entity, but the metabolic expression of a wide variety of underlying disease states. It may be the

Table 4

Histologic Diagnoses in 98 Patients Ill with the Nephrotic Syndrome and Studied by Renal Biopsy

		No. of Cases		
I.	Glomerulonephritis			46
	1. Membranous Type		28	
	Associated with superimposed pyelonephritis	3		
	Associated with severe vascular changes	2		
	Associated with margination of leukocytes (both patients were in heart failure)	2		
	Associated with sarcoidosis	1		
	Associated with subacute bacterial endocarditis	1		
	2. Mixed Type—membranous and proliferative		12	
	Associated with sarcoidosis	1		
	Associated with severe vascular changes	1		
	3. Proliferative Type		6	
	Edema appeared during organic mercurial therapy	1		
II.	"Lipoid Nephrosis"			11
	Associated with arteriosclerosis	3		
III.	Systemic Lupus Erythematosus (Lupus Nephritis)			18
IV.	Amyloidosis			3
	1. Primary		1	
	2. Secondary		2	
V.	Diabetes Mellitus			15
	1. Diffuse diabetic glomerulosclerosis		1	
	2. Diffuse and nodular diabetic glomerulosclerosis		14	
VI.	Severe Arterial and Arteriolar Nephrosclerosis			1
VII.	Increased Pressure in Renal Veins			4
	1. Renal vein thrombosis		2	
	2. Constrictive Pericarditis		1	
	3. Tricuspid stenosis		1	

result of: (a) primary renal disease, such as lipoid nephrosis or glomerulonephritis; (b) renal disease associated with systemic illnesses, such as diabetes mellitus, systemic lupus erythematosus, or amyloidosis; or (c) pressure effects on the venous system draining the kidney, e.g., renal vein thrombosis or constrictive pericarditis.

Rare causes today, but more common in the past, were infectious diseases such as secondary syphilis,[22] tuberculosis [23] and diphtheria.[24] In tropical climates the nephrotic syndrome has been reported occasionally in patients suffering from quartan malaria.[25, 26] More recently, the nephrotic syndrome

has been observed in cases of subacute bacterial endocarditis.[27] In one such case observed by us, membranous glomerulonephritis was found by renal biopsy. *Staphylococcus aureus* was grown from both the kidney tissue and the blood, and the diagnoses of subacute bacterial endocarditis and membranous glomerulonephritis were confirmed post mortem.

The nephrotic syndrome has been reported as a manifestation of an allergic process.[28] Rytand observed its occurrence in seven patients who were sensitive to poison oak.[29] The nephrotic syndrome occurred three days to two months after the appearance of the poison oak dermatitis, but it did not recur subsequently when the patients were again exposed to poison oak, and when they again developed dermatitis. Rytand emphasized that there was no evidence of a direct nephrotoxic effect of poison oak, and suggested that the nephrotic syndrome might result from sensitization. If this is true, it is difficult to understand why the nephrotic syndrome did not recur with recurrent attacks of dermatitis. The development of the nephrotic syndrome has been reported during an attack of serum sickness,[30] and it has occurred in sensitive individuals following bee stings.[31, 32] Squire studied a patient in whom an allergic pathogenesis appeared to be the probable mechanism of development of the nephrotic syndrome.[28] This patient had seven separate episodes of the nephrotic syndrome, and each responded well to cortisone. He was found to be extremely sensitive to the pollens of trees and grass, and had an eosinophilia of over 1,000/mm.^{3} The initial episode occurred while haymaking on a farm during his vacation, and all subsequent relapses occurred during the pollen season.

The nephrotic syndrome has also been reported in patients receiving drugs and chemicals, such as organic and inorganic mercury,[33, 34, 35] bismuth,[36] gold,[37, 38, 39] Tridione[40, 41] and Paradione.[42] When one considers the widespread use of all these agents, the occurrence of the nephrotic syndrome is extremely rare, and the evidence for a direct etiologic relationship is presumptive. In a single case, however, Barnett has demonstrated convincingly that the recurrent episodes and remissions of the nephrotic syndrome in his patient were directly associated with the administration and withdrawal of Tridione.[40] Several authors have reported the occurrence of the nephrotic syndrome in patients receiving prolonged treatment with mercurial diuretics,[33, 34] but the pathogenetic role of the mercurial diuretic agents has not been demonstrated satisfactorily, particularly as it appears likely that chronic heart failure may produce the nephrotic syndrome. In the renal biopsy of one such patient studied by us the tubules were dilated and lined by flattened epithelium in which regenerating tubular cells were seen. In addition, however, there was evidence of a proliferative glomerulitis. When the mercurial diuretic was withdrawn the patient's condition improved, and there was no recurrence of edema when he was treated with ammonium chloride.

Although the association of renal vein thrombosis and the nephrotic

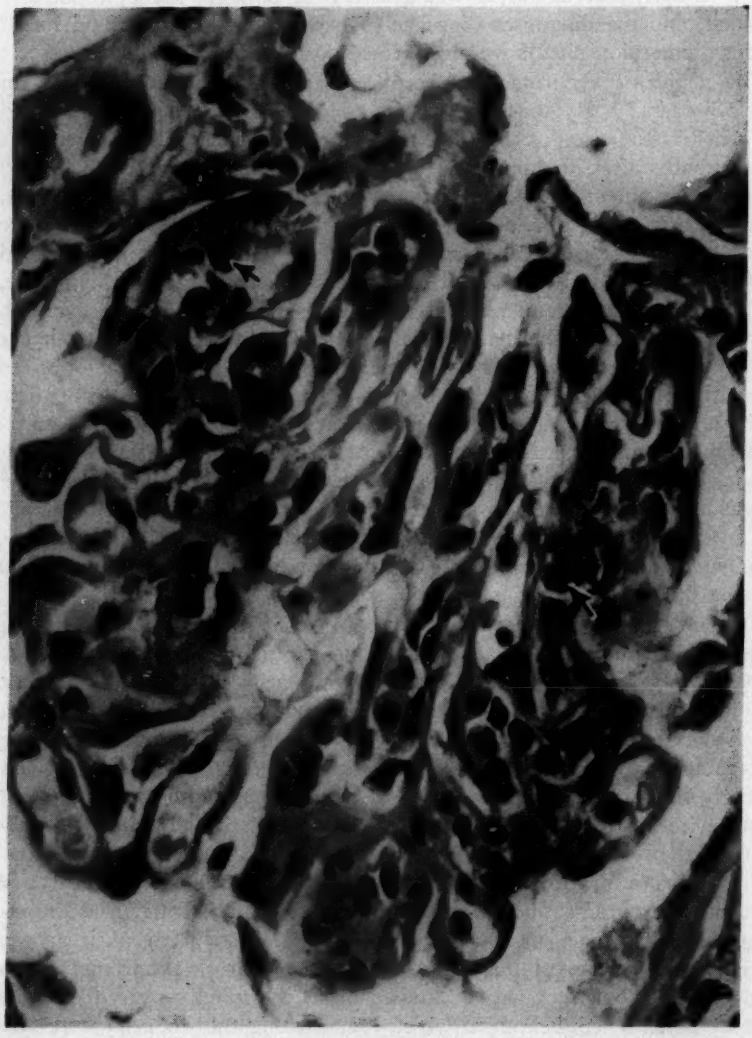

FIG. 1 (Legend on opposite page).

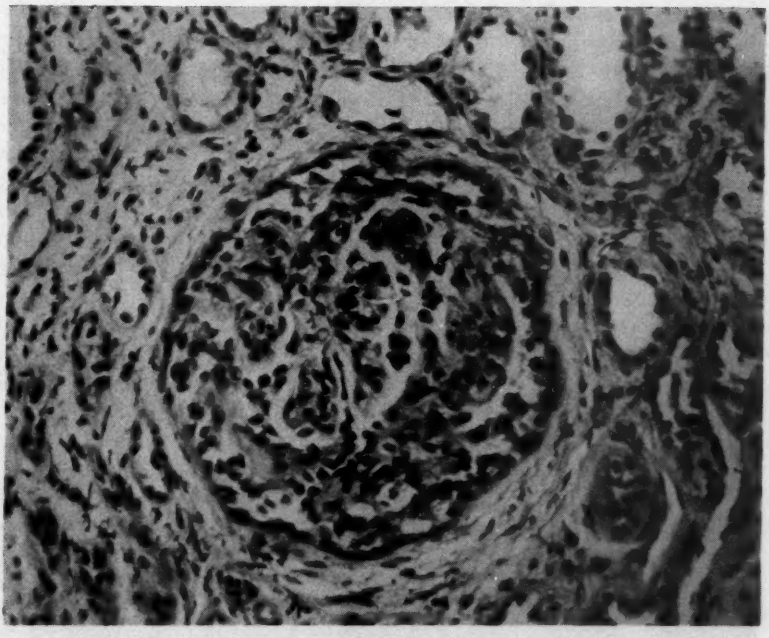

FIG. 2. *Systemic lupus erythematosus.* Renal biopsy from a 21 year old student who had been ill with systemic lupus erythematosus for 30 months. He developed generalized edema four months before the biopsy was taken. (Blood pressure, 140/108 mm. Hg; proteinuria, 3 to 10 gm./day; serum albumin, 2.4 gm./100 ml.; serum cholesterol, 460 mg./100 ml.) Advanced stage of lupus nephritis with proliferative and membranous glomerular lesions. Note the marked edema and some fibrosis in the interstitial tissue. In other glomeruli, fibrinoid changes and occasional hematoxylin bodies were seen (H & E × 300).

syndrome was first described by Rayer almost 120 years ago,[43] it is only recently that this condition has regained the attention of clinicians.[44] The main abnormality is extrarenal, and results primarily in interstitial renal edema and tubular degeneration. Diffuse thickening of the glomerular basement membrane develops, similar to that seen in cases of membranous glomerulonephritis. An unusual histologic feature seen in a number of these cases is margination of leukocytes in the glomerular capillaries.* [44] If the obstruction to the renal vein is sudden and complete no collateral cir-

* In two patients classified in table 4 as membranous glomerulonephritis, margination of leukocytes was noted in the glomerular capillaries. It is of interest that both patients were in congestive cardiac failure when the biopsies were made.

FIG. 1. *Constrictive pericarditis.* Renal biopsy from a 73 year old man with constrictive pericarditis and the nephrotic syndrome (edema, 3 plus; proteinuria, 5.4 gm./day; serum albumin, 1.2 gm./100 ml.; serum cholesterol, 327 mg./100 ml.). In this representative glomerulus there is a mild diffuse thickening of the capillary basement membrane. Note particularly the margination of polymorphonuclear leukocytes within the capillary lumina. This unusual feature was not seen in the usual type of membranous glomerulonephritis, but has been observed in the glomeruli of patients with the nephrotic syndrome due to renal vein thrombosis and congestive cardiac failure (H & E × 875).

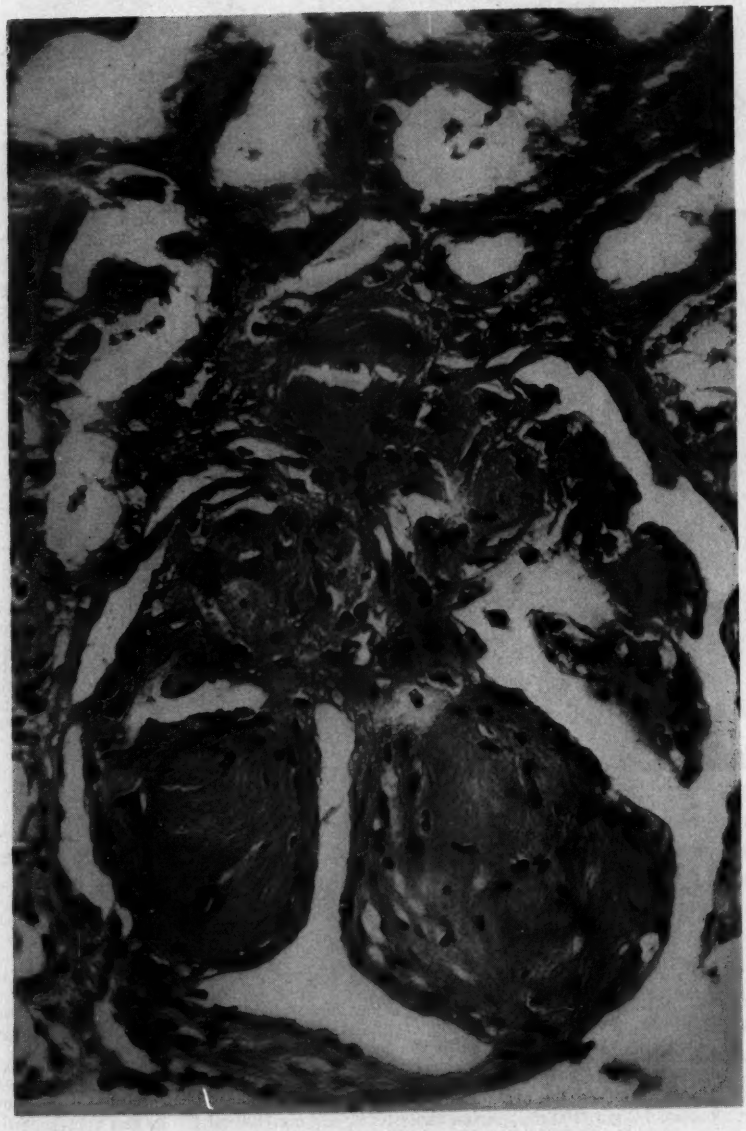

FIG. 3 (Legend on opposite page).

culation develops. The affected kidney is functionless, and the nephrotic syndrome does not appear. However, if adequate collateral venous drainage does develop the nephrotic syndrome occurs. Partial obstruction to the renal venous return may result not only from organic obstruction to the renal veins, but also from a functional obstruction due to considerable elevations of the pressure in the inferior vena cava. This may also result in the nephrotic syndrome. We have observed this in constrictive pericarditis,[45] severe congestive cardiac failure,[46] tricuspid valve disease,[47] and in thrombosis of, and pressure on, the inferior vena cava.[48] In these conditions the histology of the kidney (figure 1) is indistinguishable from that found in cases of renal vein thrombosis[49]; the conditions are of particular interest because they indicate that a simple mechanical disturbance of blood flow may initiate a complex metabolic derangement. Blainey, Hardwicke and Whitfield reported the occurrence of the nephrotic syndrome in a patient with constrictive pericarditis, in whom a pericardiectomy was done.[45] Two months after the operation the patient had no edema, the urine contained no protein, and the biochemical abnormalities had disappeared. Thus far this is the only case where it has been possible to lower the elevated inferior vena caval pressure, and to produce thereby a cure of the nephrotic syndrome.

The nephrotic syndrome occurs frequently in generalized disease processes which affect the kidney, such as systemic lupus erythematosus, diabetic glomerulosclerosis, Schönlein-Henoch purpura,[50] primary[51] and secondary amyloidosis,[4] and myelomatosis with or without amyloidosis.[46]

It is noteworthy that most of these are diseases which affect small blood vessels throughout the body. In the kidney they affect particularly the afferent arterioles and glomerular capillaries. It has also been reported to occur in polyarteritis nodosa, progressive systemic sclerosis[52] and sickle cell anemia.[52] It is not possible at the present time to be certain of the causal relationship of these three diseases to the nephrotic syndrome, as full case reports have not been presented in the literature.

The incidence of systemic lupus erythematosus appears to vary considerably from one country to another. In those areas where it has been recognized it is a common cause of the nephrotic syndrome. In our series of 98 patients with the nephrotic syndrome, lupus nephritis was the underlying cause in 18 (table 4 and figure 2). The course of the renal disease was usually rapid, and death occurred within a few months to three years in most patients so afflicted. In the more severely and acutely progressive cases the blood cholesterol levels were lower than those usually found in the

FIG. 3. *Diabetes mellitus.* Renal biopsy from a 35 year old man who had had diabetes mellitus for 13 years and edema for a few months (advanced diabetic retinopathy; blood pressure, 150/105 mm. Hg; urinary protein excretion, 6 to 18 gm./day; serum albumin, 2.4 gm./100 ml.; serum cholesterol, 522 mg./100 ml.). Representative glomerulus showing nodular and diffuse diabetic glomerulosclerosis. Note the characteristic lamination of the nodules and the sclerosis of the afferent arteriole. In the nephrotic syndrome associated with diabetes mellitus, nodular lesions are usually less prominent than in this case (H & E × 370).

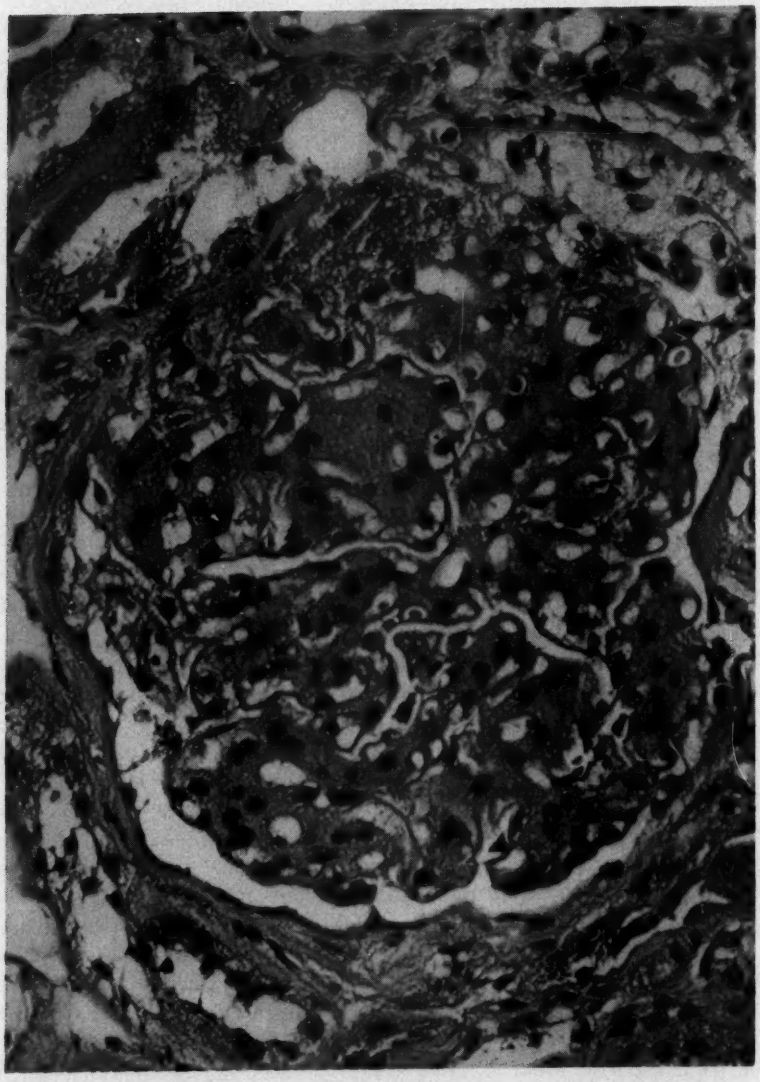

FIG. 4 (Legend on opposite page).

nephrotic syndrome, and these patients died within a few weeks or months of the onset of edema. The natural history and pathology of the nephrotic syndrome in systemic lupus erythematosus have been discussed fully elsewhere.[53]

Diabetes mellitus was the cause of the nephrotic syndrome in 15 patients (table 4). In our patients the occurrence of the nephrotic syndrome could not be related to the severity, duration or control of the diabetic state, nor was it related to the type of treatment given. In the past, attention has been focused particularly on the nodular glomerular lesion described by Kimmelstiel and Wilson.[54] In the present series these lesions (figure 3) were found in only 14 of the 15 diabetics with nephrotic syndrome. That the Kimmelstiel-Wilson lesions are not universally present in diabetics with nephrotic syndrome accords with the experience of others.[55, 56, 57, 58] It seems unlikely that the massive proteinuria characteristic of the nephrotic syndrome could be due to the nodular lesions in the glomeruli, which are often sparsely distributed. It is far more likely that the proteinuria was associated with diffuse diabetic glomerulosclerosis. Our observations [59] and those of Adams [56] support this concept, for we found the diffuse type of diabetic glomerulosclerosis described by Laipply, Eitzen and Dutra [60] and emphasized by Bell [61] in all 15 cases (figure 4). In addition, we have shown that the amount of protein in the urine is much more closely related to the severity of the diffuse lesions than to that of the nodular lesions.[59]

The nephrotic syndrome was also observed in one middle aged man who had had severe hypertension for from three to five years. When he was first seen the urine contained no protein; later, increasing amounts of protein appeared in the urine, and he ultimately developed the nephrotic syndrome. In addition to the severe tubular degeneration and interstitial edema seen in the renal biopsy sections, there were well marked sclerosis of afferent arterioles and hyaline arteriosclerotic changes in the glomeruli. These changes predominated in the hilar region of the tuft. The edematous phase was transitory, and he had a spontaneous diuresis. To our knowledge only one other case of the nephrotic syndrome associated only with arteriolar nephrosclerosis has been described.[62] Moreover when Bloom and Seegal reviewed 120 autopsies on patients who died with renal failure they found no history of the nephrotic syndrome in 50 patients who had had arteriolar nephrosclerosis.[63]

Diseases intrinsic to the kidney are the most common causes of the nephrotic syndrome. Glomerulonephritis was found in 46 of 98 patients

FIG. 4. *Diabetes mellitus.* Renal biopsy from a 31 year old woman who had had diabetes mellitus for 19 years and who had developed edema six months before the biopsy was taken (advanced diabetic retinopathy; blood pressure, 170/110 mm. Hg; proteinuria, 6 gm./day; serum albumin, 2.9 gm./100 ml.; serum cholesterol, 566 mg./100 ml.) Representative glomerulus showing moderately severe diffuse diabetic glomerulosclerosis. This type of glomerular lesion is always present when the nephrotic syndrome develops in diabetes mellitus; it is characterized by deposition of "hyaline" material within and between the capillary walls (H & E × 500).

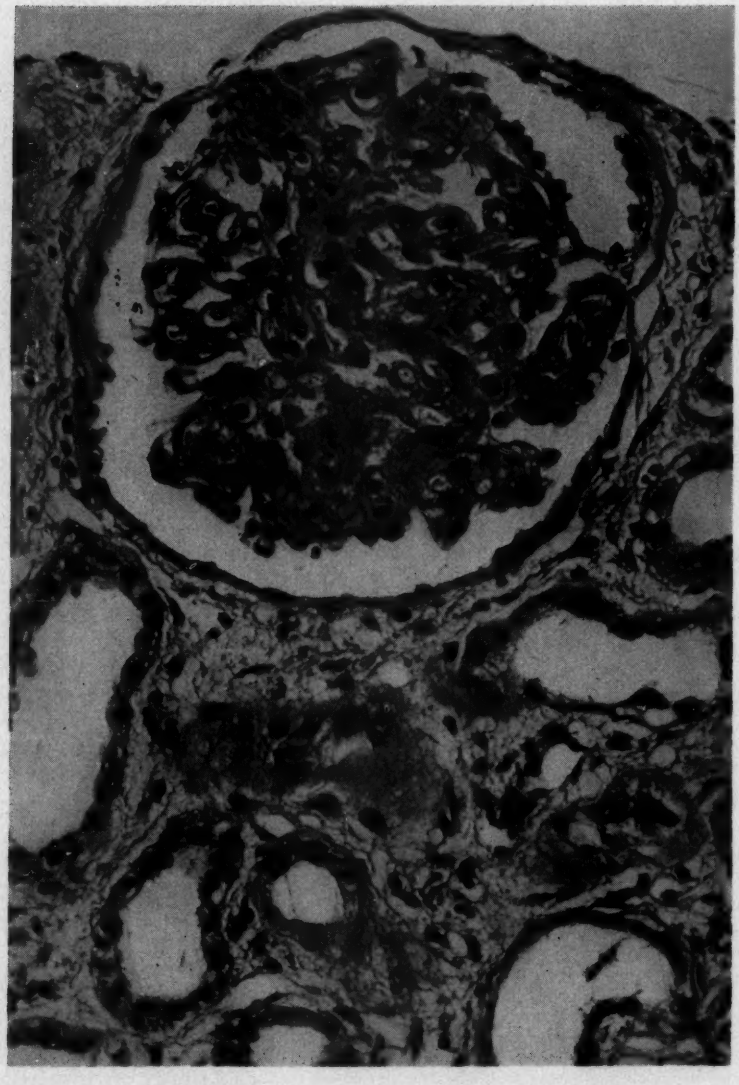

FIG. 5 (Legend on opposite page).

with the nephrotic syndrome (table 4). Although there are many histologic classifications of glomerulonephritis, we have preferred to limit our terminology to three types:

1. Membranous glomerulonephritis (figures 5 and 6), in which the pathologic change is seen predominantly or exclusively in the glomerular basement membrane (28 cases).

2. Proliferative glomerulonephritis, in which proliferation of endothelial and/or epithelial cells is the most prominent feature and in which epithelial or fibroepithelial crescents usually develop (six cases).

3. Mixed membranous and proliferative glomerulonephritis (figure 7), in which both membranous and proliferative changes were equally prominent (12 cases).

The histologic features of the first two groups correspond to Ellis' types II and I, respectively,[3] and to Longcope's types B and A.[64] It will be noted that membranous glomerulonephritis was considerably more frequent than was either of the other histologic types.

Lipoid nephrosis was originally recognized by Müller,[65] and described in detail by Munk [66] and by Volhard and Fahr.[67] The existence and nature of this entity have been the subject of controversy for many years. In essence, we understand by lipoid nephrosis a condition of unknown etiology characterized clinically by the nephrotic syndrome and having a good prognosis. The patient ultimately recovers completely unless, as was common in the past, he dies of intercurrent infection. There is no evidence of changes in the glomerular architecture by light microscopy, i.e., there is no glomerulonephritis (figure 8). However, the tubules are degenerated and filled with fat, while the interstitial tissue is edematous. Before the technic of renal biopsy was in use, it was usually impossible to make a definitive evaluation of the underlying renal pathology in many patients with the nephrotic syndrome. As a result, the diagnosis of lipoid nephrosis could be made only retrospectively many years after the edema and proteinuria had disappeared, or at the postmortem examination if the patient died of an intercurrent illness. From table 4 it can be seen that no definitive structural changes were observed in the glomeruli of 11 patients with the nephrotic syndrome when renal biopsies were made during or immediately after the edematous phase. In all there was degeneration of the tubules, the lining epithelium of which contained fat, and there was edema of the interstitial tissue. No significant abnormality could be demonstrated in the glomeruli in sections stained with hematoxylin and eosin, periodic

FIG. 5. *Membranous glomerulonephritis.* Renal biopsy from a 21 year old housewife who had had the nephrotic syndrome for four months (generalized edema; blood pressure, 130/75 mm. Hg; urinary protein excretion, 13 to 25 gm./day; serum albumin, 0.6 gm./100 ml.; serum cholesterol, 1,000 mg./100 ml.) In all glomeruli there was a diffuse, fairly regular thickening of the capillary basement membrane. Note the absence of significant glomerular hypercellularity. There is well marked edema of the interstitial tissue (H & E × 500).

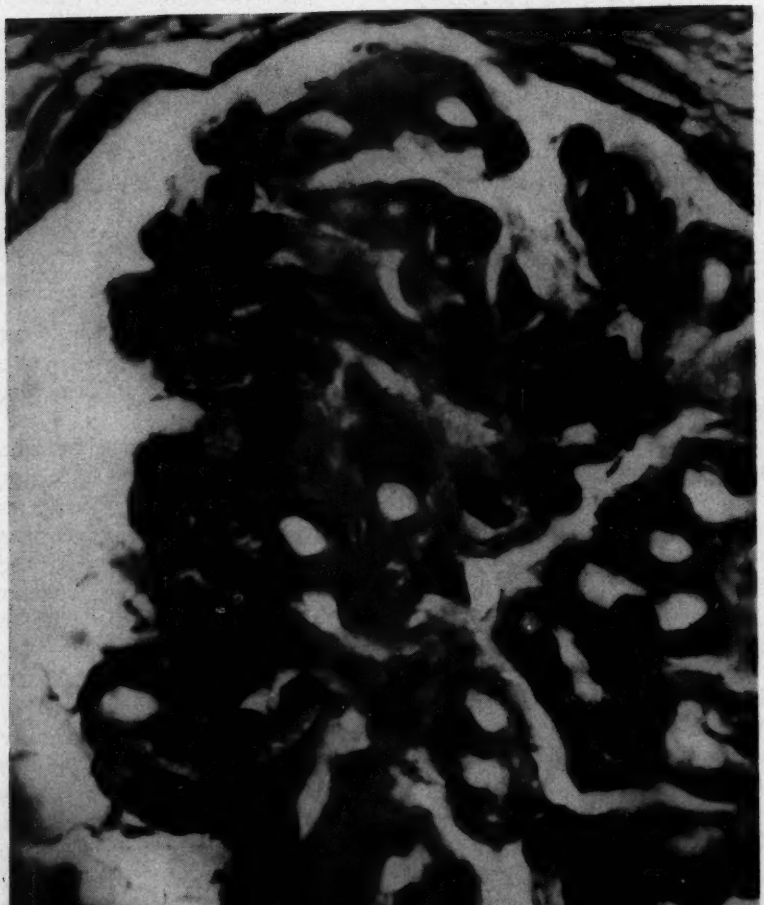

FIG. 6 (Legend on opposite page).

acid-Schiff and Mallory-azan. Clinically these patients have done well. All those treated with ACTH or adrenal corticosteroids had an excellent diuresis. No patient has developed permanent hypertension or evidence of renal failure. Proteinuria persists in some, but has disappeared completely in others.

It is at present impossible to classify these patients, either clinically or histologically. If they continue in excellent health without evidence of renal disease for many years, and if the renal histology remains normal, then we may consider that their original episode of nephrotic syndrome was truly associated with lipoid nephrosis. If, on the other hand, the glomerular basement membrane of these patients does eventually become thickened, we must consider that the nephrotic syndrome was due to early membranous glomerulonephritis. The earliest changes in the glomerular capillaries in these patients are detectable only by electron microscopy.[68, 69] From the clinician's point of view, however, the finding of normal or minimal glomerular changes in a patient with the nephrotic syndrome implies that the prognosis is considerably better than in those patients in whom the nephrotic syndrome is associated with definitive changes in the glomerular architecture.

Treatment

Treatment in the nephrotic syndrome should be directed toward the patient's principal complaint of edema, to the underlying renal condition, and to specific etiologic factors when these can be determined. At present much treatment is necessarily of a nonspecific nature, although with increasing accuracy in diagnosis this situation will change. Salt restriction is one of the most important of the measures designed to prevent edema and to initiate diuresis, and while low salt diets are widely prescribed, little attention is paid by many clinicians to ensuring that these are sufficiently low in sodium. An intake of less than 10 mEq./day (580 mg. sodium chloride) almost always prevents the accumulation of edema and will often start a diuresis, even without other forms of therapy. Limitation of salt intake to this level is now relatively easy with low sodium milk powders (Lonalac), as the diet can be given mainly in the form of drinks or, in severely edematous subjects with poor appetite, by intranasal drip feeding.

The level of protein intake required by these patients has been the cause of much argument. High protein diets of 150 gm. per day or more were originally advocated by Epstein,[70] and employed with considerable success. Later writers, however, observed a rise in the urinary protein loss on such diets,[71] and interpreted this as deterioration in the renal condition. On the

Fig. 6. *Membranous glomerulonephritis.* Renal biopsy from a 47 year old taxi driver who had been ill with the nephrotic syndrome for eight months (blood pressure, 140/70 mm. Hg; edema, 2 plus; urinary protein excretion, 12 gm./day; serum albumin, 2.7 to 4.3 gm./100 ml.; serum cholesterol, 300 to 600 mg./100 ml.). In this representative glomerulus, note the severe, diffuse thickening of the capillary basement membrane, characteristic of membranous glomerulonephritis (H & E × 1500).

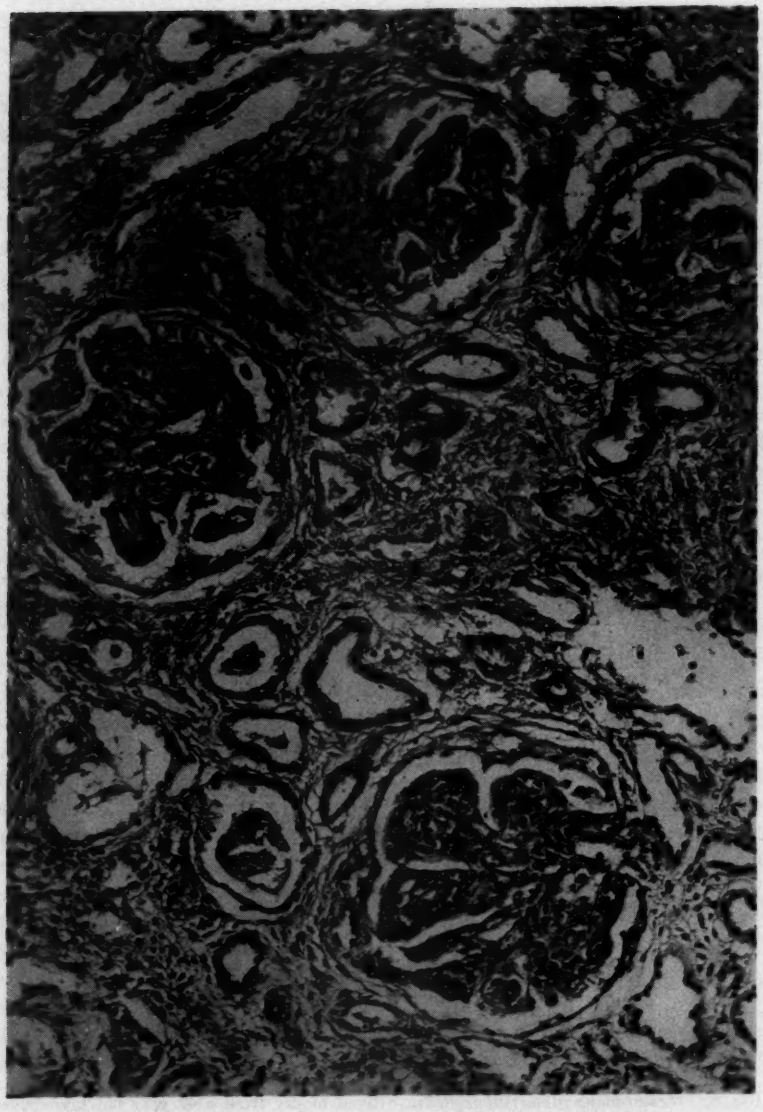

FIG. 7 (Legend on opposite page).

basis of animal studies it was also argued that high protein diets were undesirable, as the prognosis in nephrotoxic serum nephritis was worse when high protein diets were given, and the kidney was said to be required to do more "work" in excreting the additional urea load. Neither of these hypotheses is tenable, as it has been shown that increased proteinuria is to be expected with small rises of serum proteins,[72] and the work load caused by the excretion of urea is a very small fraction of that required by other tubular secretory processes in the kidney that occur normally in the nephrotic syndrome. The demonstration on high protein diets of prolonged positive nitrogen balances, at times amounting to 500 gm. nitrogen in some patients with proteinuria of many months' duration, suggests the presence of a severe body deficit of protein, of which the reduced serum proteins are only one manifestation. In adult patients no maximal level of protein intake could be observed other than that set by the patient's appetite,[73] and positive nitrogen balances were recorded with protein intakes ranging from 65 gm. to 200 gm., higher intakes leading to higher positive balance (figure 9). Since this body nitrogen deficit seems of fundamental importance in the patient with prolonged proteinuria, it would appear advisable to replace protein as rapidly as possible; in practice, it has been found that intakes of 120 gm. per day for the average adult, with high caloric intakes (50 to 60 cals./Kg.), have provided satisfactory repletion without unpalatable diets. Higher levels may be obtained on occasion with continuous tube feeding, and there seems to be no contraindication to their use. It is of course essential to ensure that patients actually take such diets; too often, high protein diets are advised but not consumed. The poor appetite of the edematous patient requires constant supervision and coaxing to ensure that adequate intakes are obtained.

In some patients with severe and prolonged proteinuria, deficiencies of both calcium and potassium may occur, with resulting bone rarefaction and hypokalemia. Both these defects are corrected by high protein diets, with the use of low sodium milk powder described, although additional potassium may be required in the early stages of treatment.

The precise value of steroid therapy in the nephrotic syndrome is still to be determined, since there has been considerable confusion in the rationale for the use of steroids, and great differences in dosage and in the type of steroid used in different reports. Many have used ACTH or cortisone in short courses for from 10 to 15 days, with large doses simply as a "diuretic," and there is little doubt that many patients will show loss of weight and edema with this treatment.[74, 75] The relapse rate, however, is

FIG. 7. *Proliferative and membranous glomerulonephritis.* Renal biopsy from a 14 year old schoolboy who gave a history of acute glomerulonephritis three months earlier, and who had had edema for two months (blood pressure, 140/70 mm. Hg; urinary protein excretion, 5 gm./day; serum albumin, 1.9 gm./100 ml.; serum cholesterol, 465 mg./100 ml.). Subacute glomerulonephritis with proliferative and membranous features. Note the fibroepithelial crescent around the glomerular tuft on the right, the marked interstitial edema, and the atrophy and dilatation of the convoluted tubules (H & E × 200).

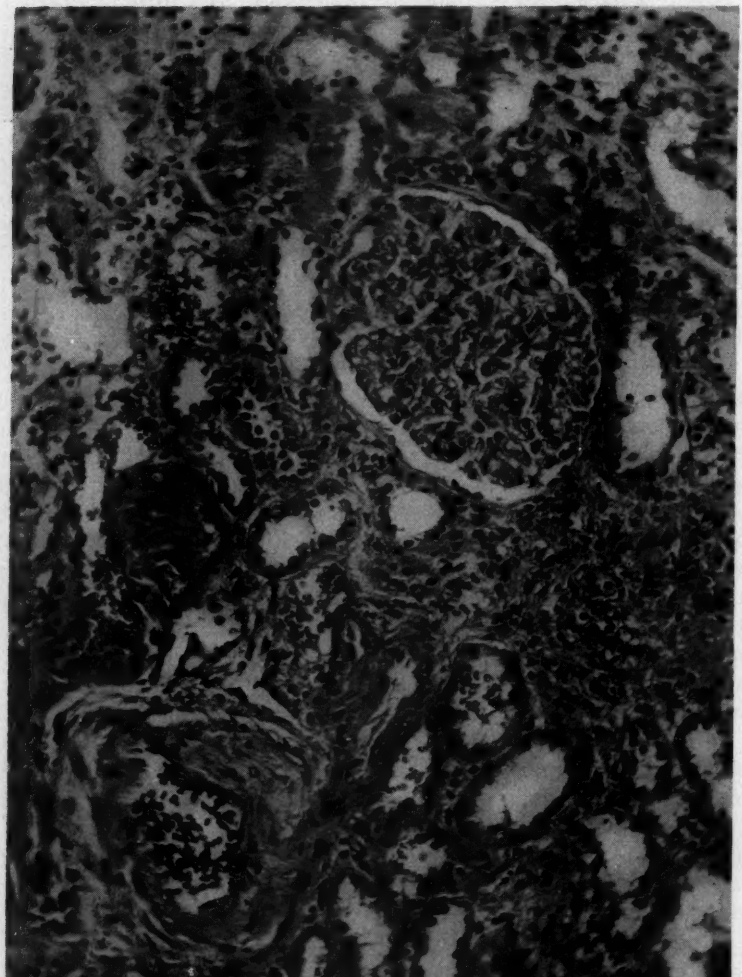

FIG. 8 (Legend on opposite page).

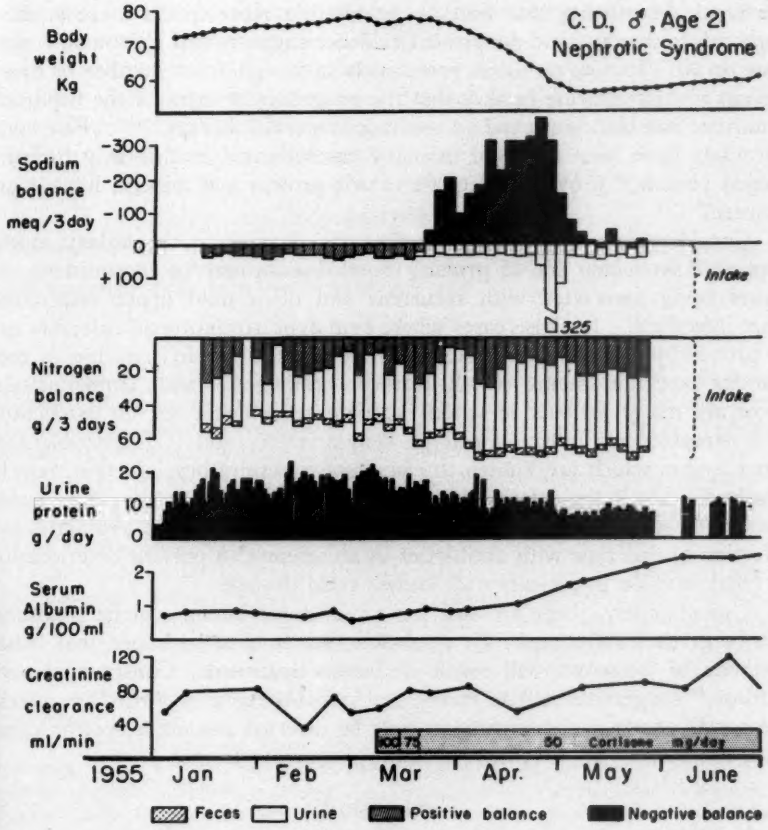

FIG. 9. Metabolic study in a 21 year old patient with the nephrotic syndrome. Note that this patient was in profound positive nitrogen balance throughout the five-month period during which he was studied—the result of an excellent intake of protein and calories.

high, and in many of the reported cases there has been little alteration in the proteinuria shortly after the cessation of a course of steroid. More prolonged treatment, either with cortisone in continuous dosage for many months,[46] or with intermittent courses three days per week for periods of from eight to 10 weeks,[75] has caused reduction in the proteinuria and decrease in the relapse rate in a number of patients; however, little reduction in the frequency of relapse was observed by Roscoe [5] in adults on intermittent dosage. While relief from edema is clearly important, alteration of

FIG. 8. *Lipoid nephrosis.* Renal biopsy from a 66 year old woman who had been ill with the nephrotic syndrome for four months (blood pressure, 160/88 mm. Hg; anasarca; urinary protein, 4 plus; serum albumin, 1.9 gm./100 ml.; serum cholesterol, 755 mg./100 ml.). The glomeruli were congested but were normal in other respects. Note the moderate arteriosclerosis and the interstitial edema (H & E × 225).

the renal abnormality that leads to proteinuria represents a more positive approach to therapy, and the present evidence suggests that continuous cortisone or ACTH does diminish proteinuria in a significant number of cases. Recent reports indicate further that the prognosis in cases of the nephrotic syndrome has been improved by continuous steroid therapy.[76, 77] Few complications have been observed in many cases treated in this way for prolonged periods,[46] provided adequate caloric protein and mineral intakes are ensured.

Considerable evidence suggests that the damage to the kidney in the nephrotic syndrome due to primary renal disease may be intermittent, relapses being associated with recurrent and often mild upper respiratory tract infections. In those cases where hemolytic streptococcal infection can be proved by throat swab or ASO titer levels, the prophylactic use of continuous penicillin seems worth further, prolonged trial. Unfortunately, there are many patients in whom no definite evidence for an association with streptococcal infection can be demonstrated, and it is possible that other agents which are known to cause upper respiratory infection may be involved. Until the relationship of specific infections to the renal lesion can be defined, it would certainly seem advisable to treat promptly any infection of this type with antibiotics in an attempt to prevent deterioration of renal function in patients with known renal disease.

Unfortunately, there are still few patients for whom specific treatment can be given for the nephrotic syndrome, but it is to be hoped that better methods of diagnosis will result in better treatment. Constrictive pericarditis,[45] congestive cardiac failure and possibly lupus nephritis are among the conditions in which treatment may be directed toward a specific cause with satisfactory improvement in the nephrotic syndrome.

Conclusion

The adult who is ill with the nephrotic syndrome comes to the doctor because he has edema. In most instances, physical examination and laboratory investigations, including tests of renal function, do not help in making a differential diagnosis. If azotemia is severe, and if renal function is markedly impaired, then one can usually predict that there is severe structural damage to the kidney. The converse does not hold: there can be marked structural changes to the glomeruli with little alteration in renal function; and with comparatively normal glomeruli, mild or moderate degrees of azotemia may be found. It is true that meticulous history taking is the best clue to the underlying disease. Nevertheless, in many patients with nephrotic syndrome the only complaint is edema. It is these circumstances that make renal biopsy so valuable a tool in the exact diagnosis of the disease—and, as has been indicated in the body of the paper, there may be a wide variety of pathologic patterns associated with the nephrotic syndrome.

As long as the physician considers that the nephrotic syndrome is a single entity with a poor prognosis, he will tend to adopt a pessimistic approach to its treatment. Discovering exactly what is wrong with the patient is useful, because it provides a rational approach to therapy, and stimulates the physician to continue to seek the latest therapeutic advances in the treatment of that particular disease.

ACKNOWLEDGMENT

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SUMMARIO IN INTERLINGUA

In adultos le syndrome nephrotic es le expression clinic de multe differente statos pathologic. Illo pote resultar ab damnification de glomerulos o de tubulos o ab augmento del pression in le venas renal. Nostre studios de biopsia renal in 98 adultos nephrotic ha reflectite un extense spectro de pathologia e de etiologia.

Glomerulonephritis subacute o chronic (membranose o proliferative o ambes) esseva trovate 46 vices. In 15 diabeticos, lesiones esseva trovate que esseva diffuse o diffuse e nodular o diffuse e nodular e exsudative. Dece-octo del patientes habeva systemic lupus erythematose.

In 11 patientes, le apparentia histologic esseva typic pro "nephrosis lipoide." Multo numerose erythrocytos esseva vidite in le glomerulos in que le membrana basal e le cellulas endothelial e epithelial esseva normal. Grados sever de degeneration tubular e de edema interstitial esseva observate. Le administration de hormones esseva sequite per un excellente diurese. Al tempore presente iste 11 patientes es vivente. Tres ha un sanitate excellente, e nulle has disveloppate signos de progressive morbo renal.

Esseva etiam observate casos de amyloidosis renal primari e secundari, de thrombosis de vena renal, de pericarditis constrictive, de insufficientia tricuspidal e stenosis, de nephrosclerosis arteriolar, e de myelomatosis sin amyloidosis. Un numero del casos esseva le resultato de diureticos mercurial. Con plus extense experientias il deveniva possibile establir exacte diagnoses histologic in plus que 90% del casos e, similemente, predicer le responsa a ACTH o corticosteroides e facer le prognose super le base del grado e del typo del compromissos glomerular.

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ELECTRONMICROSCOPIC STUDIES OF REVERSIBLE GLOMERULAR LESIONS IN THE ADULT NEPHROTIC SYNDROME *

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THE nephrotic syndrome is associated with a number of disease processes, which produce a variety of pathologic lesions in the kidney. The histology of many of these disease processes, including amyloidosis, lupus nephritis, proliferative glomerulonephritis with epithelial crescents, and renal vein thrombosis, is well known and widely accepted. On the other hand, the histologic distinction between lipoid nephrosis and membranous glomerulonephritis is still the subject of controversy. Few now agree with Munk's original description of the pathology of lipoid nephrosis,[1] namely, fatty changes in the tubules and—at least by light microscopy—normal glomeruli. Many agree with Allen [2] that ". . . 'lipoid nephrosis' is in reality a definite variety of subacute or chronic (membranous or lobular) glomerulonephritis with specific histologic alterations of the glomeruli, which are less obvious in children than in adults." Because of this confusion the etiology, clinical course and pathophysiology of these diseases are unsettled.

The studies to be reported here clarify some aspects of this controversy but, like all solutions, they raise new problems. In the last four years we have studied 98 adults with the nephrotic syndrome by renal biopsy.[3] Glomerulonephritis was diagnosed histologically in 46 instances. It was either membranous or proliferative, or mixed. In 11 other patients degeneration and fatty changes were observed in the tubules, but by light microscopy the glomeruli were considered to be within normal limits, even with the use of special stains. The ages of these patients varied from 15 to 83 years. All who were treated with ACTH or adrenal corticosteroid hormones responded

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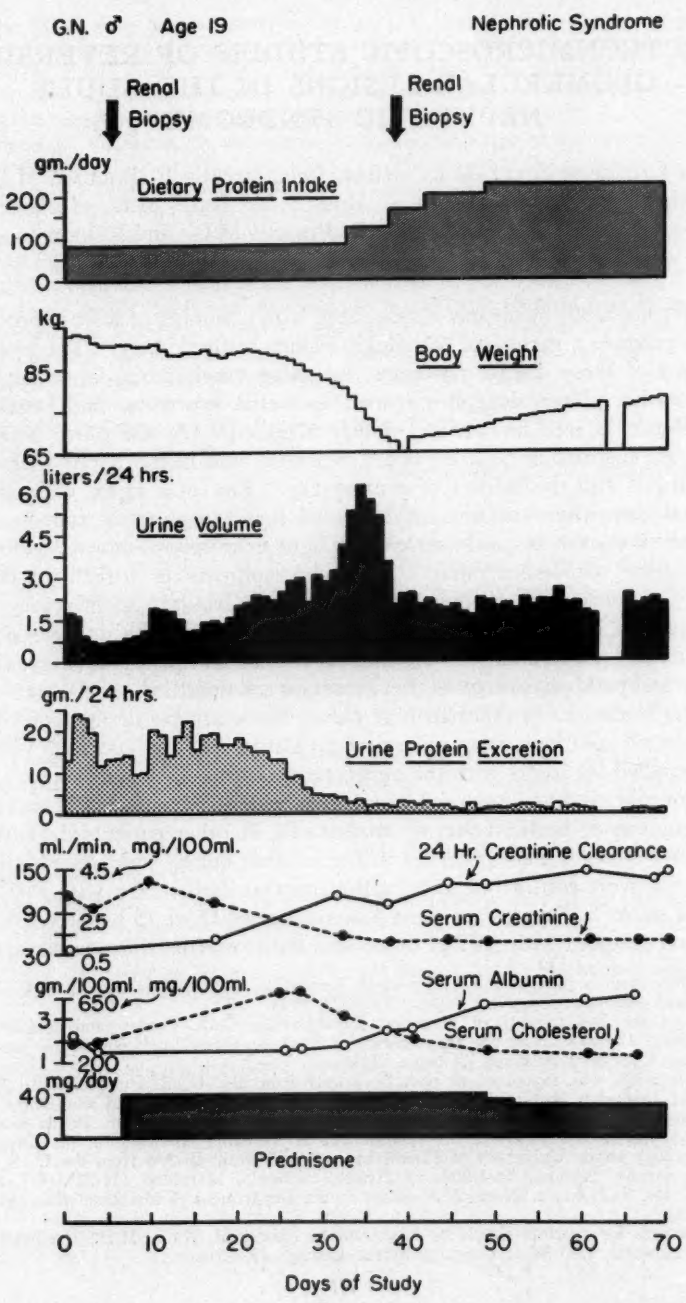
G.N. ♂ Age 19
Nephrotic Syndrome
Renal Biopsy
Renal Biopsy
gm./day
Dietary Protein Intake
200
100
0
kg.
Body Weight
85
65
liters/24 hrs.
Urine Volume
6.0
4.5
3.0
1.5
0
gm./24 hrs.
Urine Protein Excretion
20
10
0
ml./min. mg./100ml.
24 Hr. Creatinine Clearance
150
4.5
90
2.5
30
0.5
Serum Creatinine
gm./100ml. mg./100ml.
Serum Albumin
650
3
1
200
Serum Cholesterol
mg./day
40
0
Prednisone
0 10 20 30 40 50 60 70
Days of Study

FIG. 1.

with an excellent diuresis. When evaluated clinically, biochemically, and by means of serial renal biopsy, no evidence of progressive renal disease was found in periods of observation of up to three and one-half years.

To define more precisely the pathology of the glomeruli of these patients, electronmicroscopic studies were made. To date, single studies have been made on four patients, and serial studies on three others. In this paper we will present detailed clinical, histologic and electronmicroscopic observations on one patient whose glomerular lesions could be demonstrated only by electronmicroscopy. These lesions were restored to normal by treatment with prednisone.

Case Report

A 19 year old schoolboy became somewhat fatigued in January, 1957. He was otherwise in excellent health until March 8, when he had a "cold" and sore throat. Swelling of the face was first observed three days later, and by March 15 he had developed generalized edema and noted some oliguria. Much protein and a few casts were found in the urine. His blood pressure was reported to be 150/100 to 180/100 mm. of Hg. He was fed a diet low in protein and sodium, and was given penicillin. On March 20 and 21 he had injections of 80 units ACTH. There was no past history of renal disease.

On March 22, 1957, the patient was admitted to the University of Illinois Hospital. He was a large, strapping, well built young man (weight, 93.5 Kg.; best previous weight, 83.9 Kg.). Generalized edema was obvious, but neither ascites nor pleural effusion was found. His blood pressure was 160/90 mm. of Hg. No other abnormalities were detected on physical examination. The hematocrit was 50%; leukocyte count, 12,500/mm.^{3} (normal differential count); erythrocyte sedimentation rate, 15 mm. in one hour. The urine specific gravity was 1.016; 14.8 gm. protein was found in a 24-hour specimen, and the urinary sediment contained a few red and white blood cells, many hyaline, granular and cellular casts, and a few fatty casts and oval fat bodies. The results of other laboratory tests were as follows: serum creatinine, 3.30 mg./100 ml.; nonprotein nitrogen, 150 mg./100 ml.; albumin, 2.2 gm./100 ml.; globulin, 1.7 gm./100 ml.; gamma globulin, 0.60 gm./100 ml.; cholesterol, 360 mg./100 ml.; cholinesterase, 1.42 ΔpH units/hour; calcium, 6.8 mg./100 ml.; inorganic phosphorus, 6.3 mg./100 ml.; potassium, 6.2 mEq./L. The 24-hour creatinine clearance was 39 ml./minute, and the antistreptolysin O titer was 100 units. The patient was treated with a diet calculated to contain 80 gm. protein and 9 mEq. sodium per day. On the eighth hospital day treatment with prednisone (40 mg. daily) was started. The patient's urine volume began to increase 12 days later, and diuresis was complete 32 days after the prednisone was started. In all, he lost 26.9 Kg. Details of the urine volume, proteinuria, body weight, biochemical changes and treatment are given in the accompanying chart (figure 1). After the diuresis the dietary intake of protein was gradually increased to about 225 gm. daily. The patient was extremely hungry and needed no persuasion to eat all the food presented to him. He gained weight steadily and on discharge from hospital at the end of 70 days he

Fig. 1. *Chart of Clinical Course in G. N.* When the patient entered hospital he was edematous (weight, 93.5 Kg.). The serum creatinine was 3.30 gm./100 ml. and the creatinine clearance was 39 ml./minute. Treatment with prednisone was started on the eighth hospital day, and diuresis was complete on the fortieth day. Note the great decrease in the urinary protein excretion and the return to normal of the serum creatinine and the creatinine clearance, and of the serum albumin and cholesterol. Renal biopsies were done before treatment was started and when the diuresis was complete.

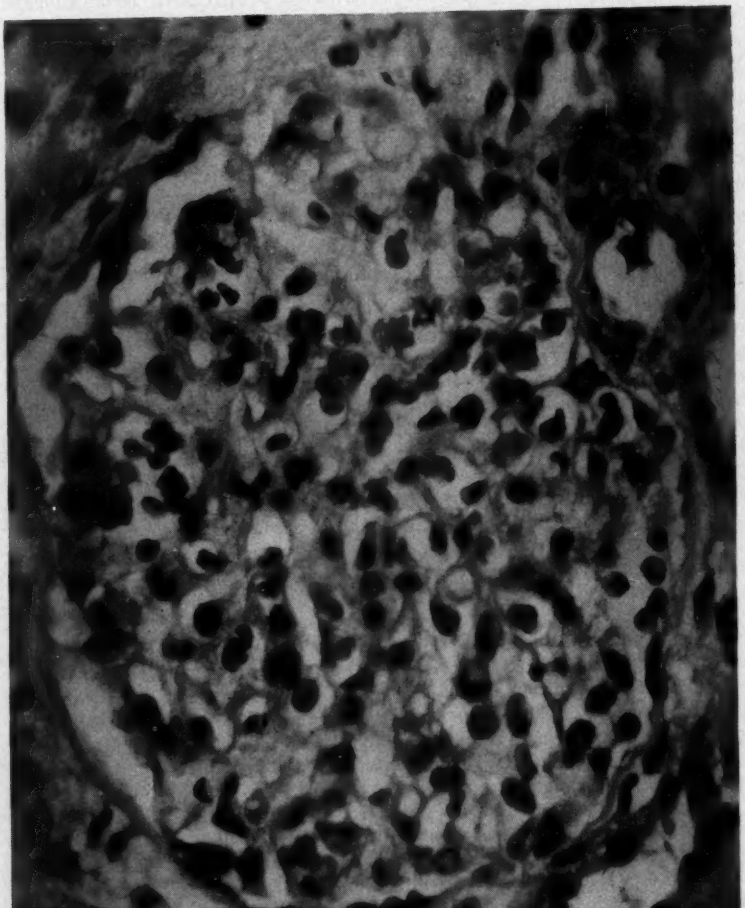

FIG. 2. *G. N. Biopsy No. 1 (Light microscopy H & E × 700).* The glomerulus is swollen and almost completely fills Bowman's space. There is no hypercellularity, and obvious thickening of capillary basement membrane could not be detected either in H & E or in PAS preparations.

weighed 77.9 Kg. After the start of treatment with prednisone the quantity of protein in the urine gradually decreased to 1 to 2 gm. daily; no cells were seen in the urinary sediment, and the number of casts decreased considerably. The serum albumin level increased to 4 gm./100 ml., and the cholesterol decreased to 230 mg./100 ml. The nonprotein nitrogen fell from 150 mg./100 ml. to normal. The creatinine clearance rose from 39 ml./minute to 144 ml./minute. The blood pressure was unchanged at 160/90 mm. of Hg.

After the patient was discharged from hospital treatment was continued at home with prednisone, 30 mg. daily, and a diet high in protein and low in sodium. On August 27 the dosage of prednisone was reduced to 25 mg. daily. On November 18, 1957, the patient entered hospital again for study. He appeared to be in excellent health and had no symptoms. His weight was 83.4 Kg. He had a moon face, slight facial acne, and purple striae on the trunk and thighs. No other abnormality was detected on physical examination. The blood pressure was 135/75 mm. of Hg.

The hematocrit was 48%; the urine specific gravity was 1.024 after withholding fluids for 12 hours. Two 24-hour urine specimens contained zero and 300 mg. of protein, and microscopic examination of the urinary sediment was normal. The results of other laboratory tests were as follows: serum creatinine, 1.10 mg./100 ml.; albumin, 5.25 gm./100 ml.; globulin, 2.35 gm./100 ml.; cholesterol, 180 mg./100 ml.; cholinesterase, 1.17 ΔpH units/hour. The 24-hour creatinine clearance was 144 ml./min.

Renal Biopsies: Three renal biopsies were obtained, the first on the sixth hospital day, when the patient was very edematous, and before starting treatment with prednisone; the second on the thirty-ninth day, i.e., after 31 days of treatment with prednisone, when he had lost all his edema; the third eight months after the onset of his illness, when he was clinically completely well.

Studies by Light Microscopy

The routine histologic studies were made on formalin fixed tissue stained with hematoxylin and eosin, periodic acid-Schiff, Mallory Azan and Oil-red-O.

The first biopsy contained cortex but no medulla (figure 2). Many of the glomeruli were swollen and almost completely filled Bowman's spaces. The glomerular basement membrane did not appear abnormal with the periodic acid-Schiff stain. The endothelial cells were present in normal numbers, and appeared to be slightly swollen. Slight proliferation of epithelial cells was noted in one or two glomeruli. There were marked swelling and granular degeneration of the lining epithelium of the convoluted tubules, which contained a moderate amount of fine granular lipid. A few tubules were atrophic. There was some edema of the interstitial tissue, but no fibrosis and no infiltration by chronic inflammatory cells. The small arteries and arterioles were normal.

Sections of methacrylate embedded tissue cut at 2 microns and stained with methylene blue were also studied. In these sections the basement membrane was thin and delicate, and no obvious changes were seen in the endothelial or epithelial cells.

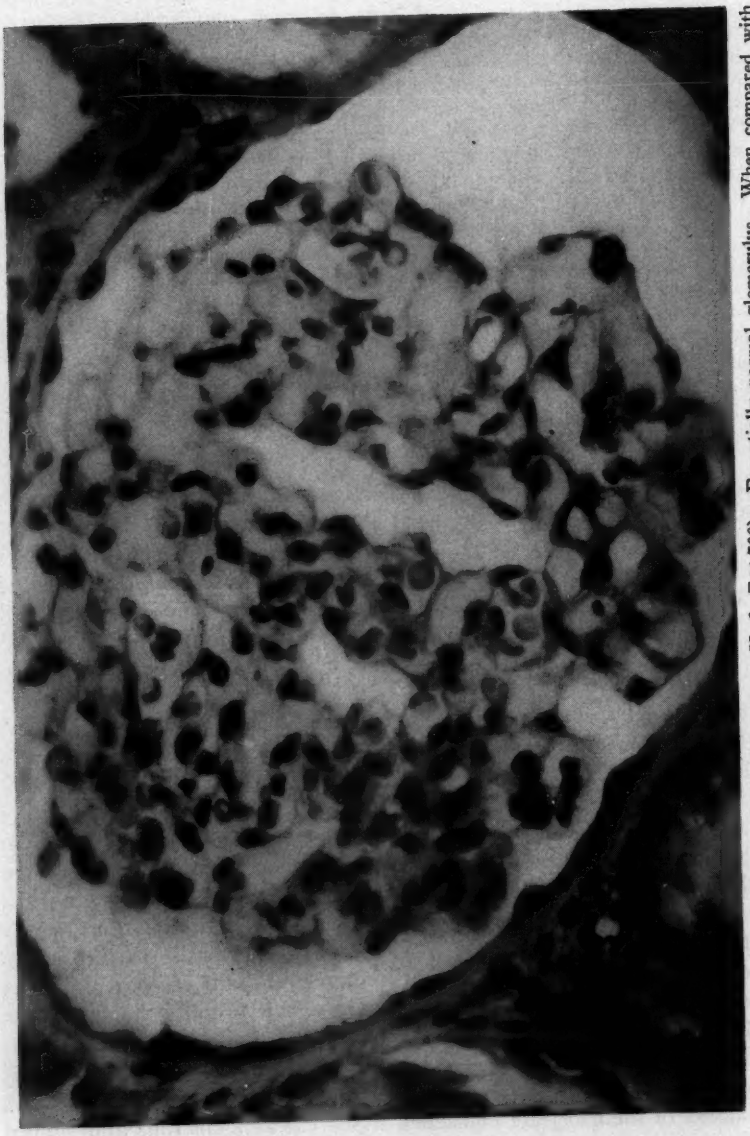

FIG. 3. *G. N. Biopsy No. 2 (Light microscopy H & E × 700).* Essentially normal glomerulus. When compared with the first biopsy the absence of swelling and the wide Bowman's space will be noted.

The second biopsy also contained cortex but no medulla (figure 3). The glomeruli were fairly large. In some glomeruli it was difficult to tell whether the basement membrane was absolutely normal. There was no hypercellularity. There were mild degenerative changes in the cells of the convoluted tubules, which contained some fine granular lipid. The interstitial tissue and small arteries and arterioles were normal.

Sections of methacrylate embedded tissue cut at 2 microns were also studied. No obvious changes were seen in the epithelial or endothelial cells. *Minute finger-like projections were noted on the epithelial side of the basement membrane of some loops; these had not been present in the first biopsy.* In some glomeruli it was impossible to tell whether the basement membrane was absolutely normal.

The third biopsy contained cortex and medulla. There was no hypercellularity of the glomeruli. In some glomeruli it was difficult to tell whether the basement membrane was absolutely normal. Bowman's capsule was slightly thickened around an occasional glomerulus. Mild degenerative changes were observed in the cells of the convoluted tubules, which contained proteinaceous material. A few groups of tubules were moderately atrophic and had a thickened basement membrane. Some convoluted tubules and many of the collecting tubules contained hyaline casts. Interstitial fibrosis was observed in a few areas near atrophic tubules. Small clumps of chronic inflammatory cells were seen around one glomerulus. The small arteries and arterioles were normal.

In summary, minor abnormalities were observed in some glomeruli in the first biopsy; no definite abnormalities were observed in the glomeruli of the second and third biopsies. Degeneration and fatty changes were prominent in the convoluted tubules in the first biopsy, but were only of slight degree in the second and third biopsies. A few atrophic tubules surrounded by small areas of interstitial fibrosis were noted in the third biopsy.

Studies by Electronmicroscopy

Before describing the abnormalities found in this case, we will summarize briefly the findings in normal glomeruli. These are based on a study of glomeruli from renal biopsy specimens taken from four patients with no evidence of renal disease. Most of the features we observed were in agreement with the descriptions of others [4, 5, 6, 7, 8, 9, 10, 11, 12, 13] in mammals and man (figures 4 and 5).

1. *Bowman's capsule:* This was formed by a basement membrane and a layer of epithelial cells. The basement membrane had a lamellar and fibrillar structure. The lining epithelium was flat, and the cytoplasm, except around the nucleus, was very thin.
2. *Glomerular tufts:* In the glomerular tuft three distinct elements were readily recognized: epithelial cells, basement membrane and endothelial cells.

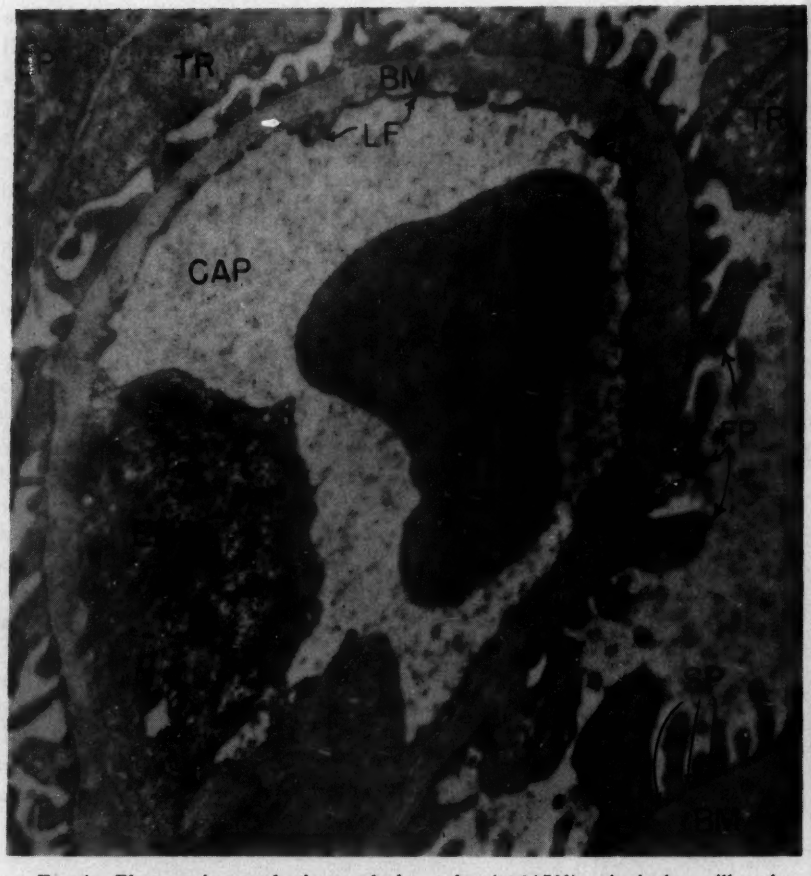

FIG. 4. *Electronmicrograph of normal glomerulus* (× *26,700*). A single capillary loop containing a red blood cell. The basement membrane (lamina densa) is homogeneous. Below and to the left are an endothelial cell nucleus and its surrounding cytoplasm, which project into the capillary lumen. An attenuated layer of endothelial cytoplasm (lamina fenestrata) lines the inner surface of the basement membrane. Regularly spaced, discrete foot processes (pedicels of epithelial cells cover the outer (capsular) surface of the membrane. The foot processes are in close proximity to the basement membrane, and are separated from one another by small spaces (slit pores). Part of the nucleus of the epithelial cell (podocyte) is seen in the upper left corner, and there are two trabeculae in the upper left and right corners.

BM = Basement membrane (lamina densa)
CAP = Capillary lumen
END = Endothelial cell
LF = Lamina fenestrata (attenuated endothelial cytoplasm)
EP = Epithelial cell (podocyte)
FP = Foot processes (pedicels) of epithelial cell
TR = Trabecula of epithelial cell
SP = Slit pores
RBC = Red blood cell
OB = Osmiophilic "bodies"

2.1. *Epithelial cells* (*Podocytes*) lay in Bowman's space and were closely applied to the basement membrane. The cytoplasm of these complex cells branched into large trabeculae, from which numerous delicate foot processes (pedicels) arose. These interlocking pedicels extended to and covered the basement membrane. They were regularly distributed, and were separated from one another by small spaces, about 80 Å wide.[5]

2.2. *Basement membrane* (*Lamina Densa*) was about 1400 Å thick. It was homogeneous and contained no fibrils or lamellar structure[5]; it is believed by some to be condensed ground substance—a macromolecular gel rich in polysaccharides.[14]

2.3. *Endothelial cells* were three to four times more numerous than epithelial cells. They lay on the capillary side of the basement membrane and bulged into the capillary lumen. Their small, dense nuclei were surrounded by a layer of cytoplasm. At some distance from the nucleus the endothelial cytoplasm, which completely invested the endothelial surface of the lamina densa, was a very thin sheet, in which many regularly distributed circular fenestrations, each about 400 Å in diameter, were seen (lamina fenestrata). The existence of a third type of glomerular cell—the mesangial cell—is still the subject of controversy among pathologists and electronmicroscopists.

First Biopsy (*figures 6 and 7*). It is fitting to recall that, when the first biopsy was made, the patient was very edematous, the nonprotein nitrogen was 101 mg./ml., the 24-hour creatinine clearance was 39 ml./minute, and the urine contained 10 to 24 gm. protein per 24 hours.

In order to study a representative sample, seven glomeruli were examined. Similar alterations were observed in all. The most striking changes were seen in the podocytes. Their pedicels had disappeared and were replaced by a continuous layer of epithelial cytoplasm of irregular thickness. This abnormal epithelial cytoplasm was clearly distinguished from the lamina densa by their different affinities for osmium. In a few areas some pedicels were recognized. However, even these were abnormal, since they appeared to be fused and not clearly separated from one another. The perinuclear cytoplasm of the podocytes and the trabeculae contained an abnormal number of vacuoles of varying size, and in some areas the trabeculae—which never encroach on the lamina densa in the normal glomerulus—were seen lying directly upon the lamina densa. A large number of small osmiophilic "bodies" were seen in the capsular spaces. They varied in size and shape, being round, oblong or oval, and had a definite limiting membrane. They were irregularly distributed, and most appeared to be lying free in the capsular space. A few were joined to the trabeculae.

The changes observed in the podocytes were striking; by contrast, no abnormality was detected in Bowman's capsule, in the glomerular basement

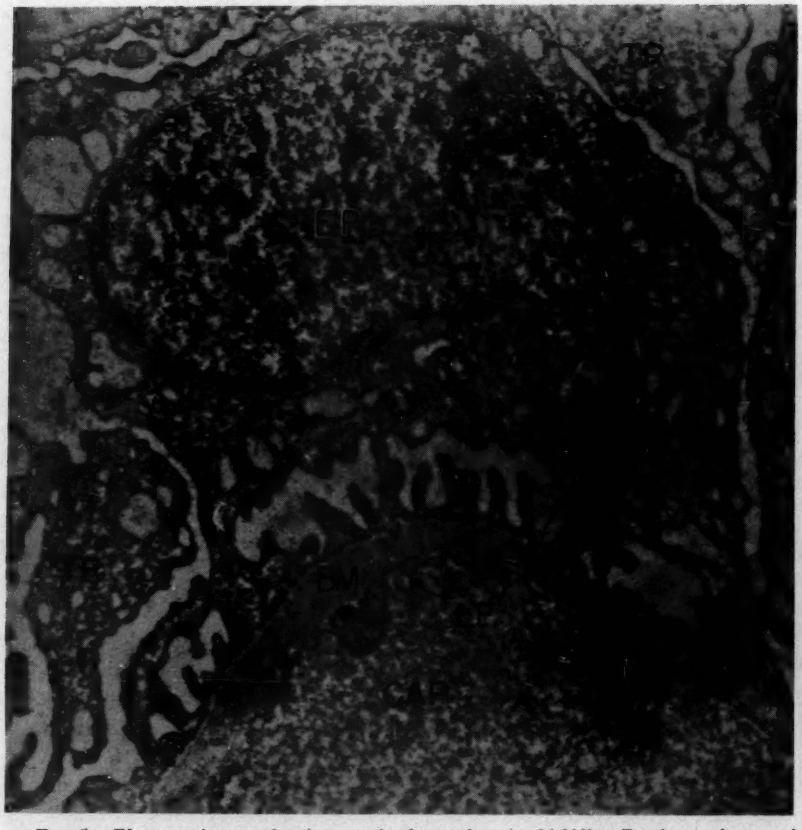

FIG. 5. *Electronmicrograph of normal glomerulus* (×*21,300*). Portions of an epithelial cell and of a capillary loop. The basement membrane is homogeneous, and on its inner surface the attenuated endothelial cytoplasm is seen. The epithelial cell nucleus is surrounded by cytoplasm from which the trabeculae and foot processes arise. The foot processes are in close proximity to the basement membrane, and are separated from one another by small spaces (slit pores).

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membrane or in the endothelial cells. These structures were also normal in the second and third biopsies. The glomerular basement membrane (lamina densa) was of normal thickness; it was homogeneous and structureless, and of fairly even density and osmiophilia. The endothelial cells were

found in normal numbers. Their cytoplasm and nuclei appeared to be normal, as did the lamina fenestrata.

Second Biopsy (*figure 8*). When the second biopsy was made the patient had been treated with prednisone (40 mg. daily) for 31 days; he

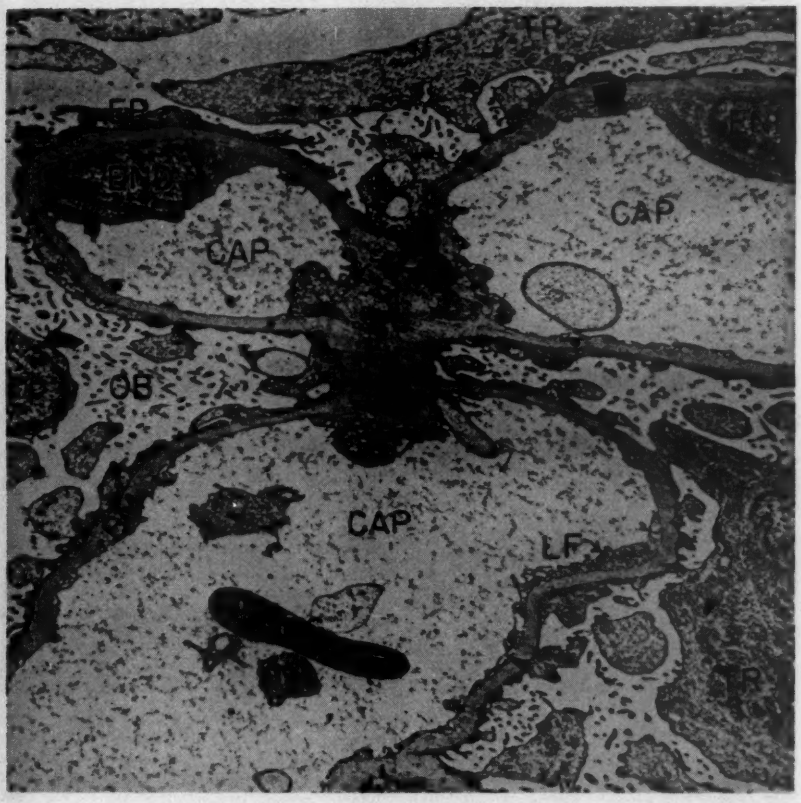

FIG. 6. *G. N. Biopsy No. 1. Electronmicrograph* (×*6600*). Three capillary loops are seen. The endothelial cells and their attenuated layer of cytoplasm are normal. The basement membrane is thin and homogeneous. The abnormalities are seen in the epithelial cells. Note that an irregular layer of epithelial cytoplasm lies along the epithelial surface of the capillary basement membrane; this layer has replaced the discrete foot processes. Within the capsular space are many small, rounded or elongated structures (osmiophilic "bodies").

BM = Basement membrane (lamina densa)
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OB = Osmiophilic "bodies"

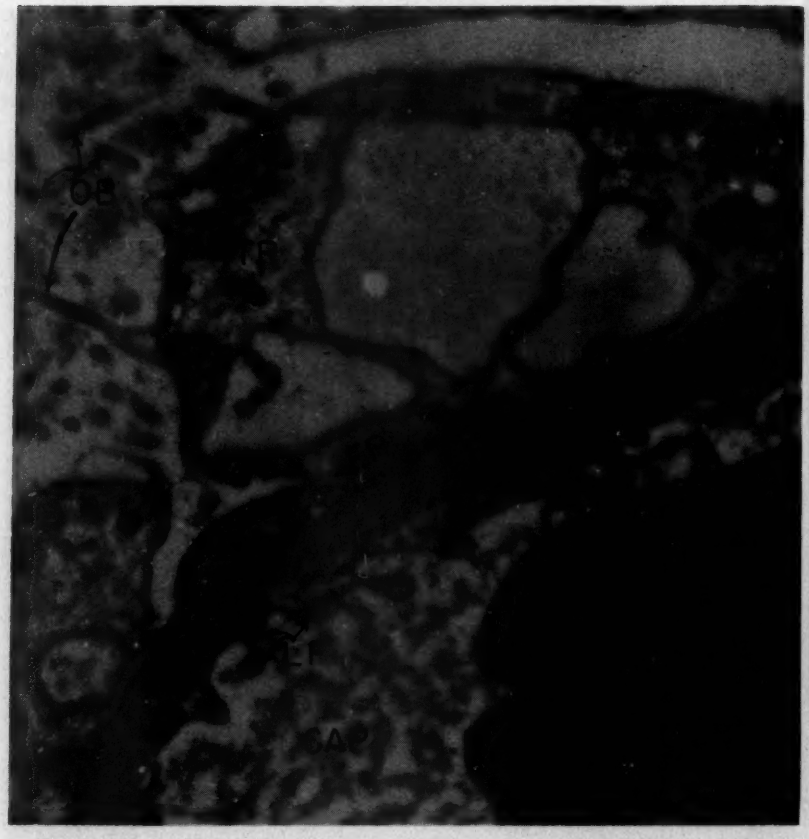

FIG. 7. *G. N. Biopsy No. 1. Electronmicrograph* (×*25,700*). Higher magnification, showing portion of a capillary loop containing red blood cells. The homogeneous basement membrane and attenuated endothelial cytoplasm are clearly seen. Note the continuous but irregular layer of epithelial cytoplasm covering the basement membrane, and the absence of foot processes. On the left is seen a collapsed trabecula in direct opposition to the basement membrane.

BM = Basement membrane (lamina densa)
CAP = Capillary lumen
END = Endothelial cell
LF = Lamina fenestrata (attenuated endothelial cytoplasm)
EP = Epithelial cell (podocyte)
FP = Foot processes (pedicels) of epithelial cell
TR = Trabecula of epithelial cell
SP = Slit pores
RBC = Red blood cell
OB = Osmiophilic "bodies"

had lost all his edema; the nonprotein nitrogen was now normal; the 24-hour creatinine clearance was normal at 96 to 126 ml./minute; and the protein excreted in the urine had decreased to about 2 gm. or less per 24 hours.

Five Glomeruli Were Examined. They were now almost normal; in

particular, only minimal abnormalities were seen in the podocytes. The pedicels were clearly seen covering the lamina densa of almost all capillary loops. Most were normal, but some were not quite distinctly separated from one another at the point adjacent to the lamina densa. The trabeculae and

FIG. 8. *G. N. Biopsy No. 2. Electronmicrograph* (×*15,000*). *After treatment with prednisone.* Portions of two capillary loops. The endothelial cytoplasm and homogeneous basement membrane are normal. Note the restoration of foot processes along the epithelial surface of the basement membrane; in most areas they are almost but not quite discrete from one another. Osmiophilic "bodies" are still present but in lesser numbers than in the first biopsy.

BM = Basement membrane (lamina densa)
CAP = Capillary lumen
END = Endothelial cell
LF = Lamina fenestrata (attenuated endothelial cytoplasm)
EP = Epithelial cell (podocyte)
FP = Foot processes (pedicels) of epithelial cell
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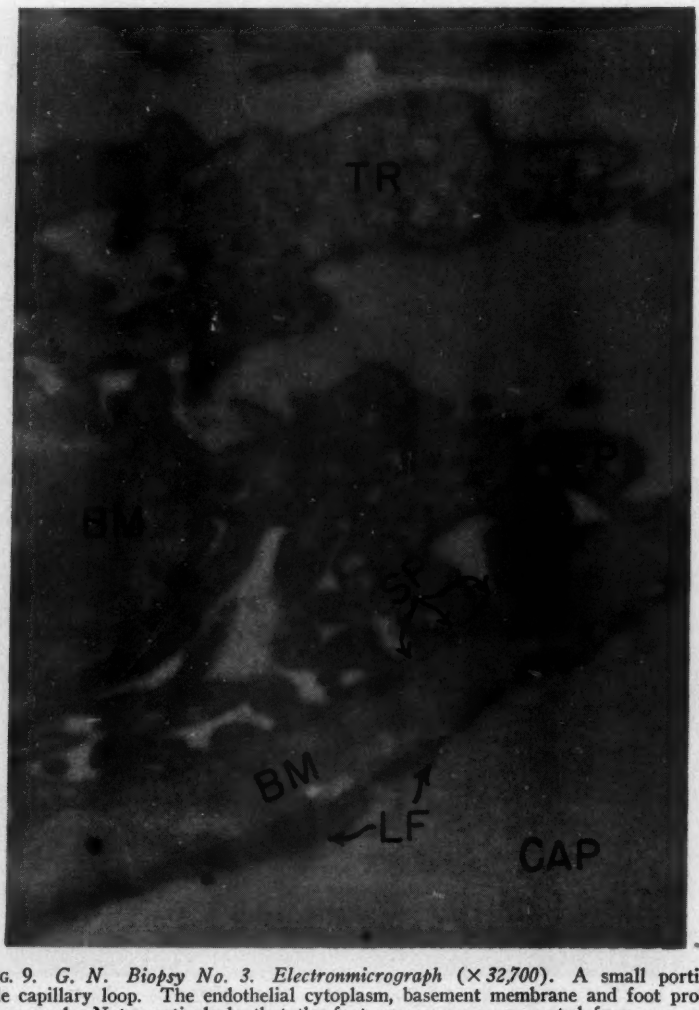

FIG. 9. *G. N. Biopsy No. 3. Electronmicrograph* (×*32,700*). A small portion of a single capillary loop. The endothelial cytoplasm, basement membrane and foot processes are all normal. Note particularly that the foot processes are separated from one another by slit pores.

BM = Basement membrane (lamina densa)
CAP = Capillary lumen
END = Endothelial cell
LF = Lamina fenestrata (attenuated endothelial cytoplasm)
EP = Epithelial cell (podocyte)
FP = Foot processes (pedicels) of epithelial cell
TR = Trabecula of epithelial cell
SP = Slit pores
RBC = Red blood cell
OB = Osmiophilic "bodies"

perinuclear cytoplasm of the podocytes appeared to be normal. A few osmiophilic "bodies" were seen in the capsular space.

Third Biopsy (figure 9). When the third biopsy was made the patient was still being treated with prednisone (25 mg. daily); he was in excellent health; the blood pressure was 136/75 mm. of Hg; the 24-hour creatinine clearance was 144 ml./minute, and the urine protein excretion was 0 to 300 mg. per 24 hours.

The glomeruli now appeared to be quite normal. The podocytes and their processes were also normal; in particular, their pedicels were lying regularly along the lamina densa, and were separated distinctly from one another at their insertion on the basement membrane.

Osmiophilic "Bodies." Before treatment many osmiophilic "bodies" were seen in the capsular space; they were still present but in lesser numbers in the second biopsy taken after diuresis; they were rarely seen and only in normal numbers in the third biopsy. The osmiophilic "bodies" appeared to be a part of the podocytes for the following reasons: (1) some were seen to be part of the trabeculae or perinuclear cytoplasm; (2) they had a limiting membrane similar to that of the pedicels and trabeculae; (3) the degree of osmiophilia was comparable to that of the pedicels and trabeculae; (4) if they were lying free in the capsular space and if they had not been attached to or part of the podocyte they would have been removed by the flow of glomerular filtrate or would have sedimented together in clumps; and (5) a few similar "bodies" have been seen in some serial sections of normal pedicels cut at 200 Å.[15] In essence it is clear that the large number of osmiophilic "bodies" were a manifestation of the general structural changes observed in the podocytes.

In summary, the lamina densa and endothelial cells were normal in all three biopsies. The podocytes were grossly abnormal in the first biopsy, almost normal in the second, and completely normal in the third. The abnormalities of the podocyte were: replacement of the pedicels by an abnormal layer of podocytic cytoplasm, vacuolation of perinuclear and trabecular cytoplasm, and the presence in the capsular space of large numbers of osmiophilic "bodies."

Discussion

It was obvious that the patient was ill with the nephrotic syndrome. As his blood pressure was 160/90 mm. of Hg, and as there was evidence of severe impairment of renal function, most clinicians would have considered his illness to be a clear cut example of severe glomerulonephritis. Although considerable tubular damage and much interstitial edema were found in the first renal biopsy, the glomeruli did not appear to be abnormal by light microscopy. In particular, there was no thickening of the glomerular basement membrane. This histologic finding—viz., normal glomeruli in biopsies from adults with the nephrotic syndrome—has been reported previously by ourselves and by others.[3, 16, 17, 18, 19, 20] A massive diuresis occurred

and was complete 31 days after starting treatment with prednisone, and renal function returned to normal; there were less degeneration and fatty change in the tubular epithelium of the second biopsy specimen, and interstitial edema was no longer observed. The glomeruli remained normal.

It was only by electronmicroscopy that abnormalities were found in the glomeruli. In the first biopsy the architecture of the epithelial cells or podocytes was profoundly altered; in particular, the pedicels were absent, being replaced by a continuous layer of podocytic cytoplasm. These findings are similar to those depicted by Piel [21] and described by Farquhar et al.[22] in young children with "nephrosis." In the second biopsy, following treatment with prednisone, the podocytes were restored toward normal and pedicels had reappeared. They were completely normal when the third biopsy was done some eight months after the onset of his illness. The endothelial cells and basement membrane were normal in all three biopsies.

The clinical, histologic and electronmicroscopic findings have been described in detail, but no diagnosis has been offered. We must conclude from the histology that there was no evidence of glomerulonephritis. In this patient, the occurrence of the nephrotic syndrome without histologic evidence of glomerular lesions leads us to diagnose "lipoid nephrosis" in an adult. This is a nonfatal illness characterized by one or more episodes of the nephrotic syndrome in which no glomerular damage would be found by light microscopy post mortem, were the patient to die of a complicating disease. Ultimate proof of the diagnosis of "lipoid nephrosis" must await a prolonged period of observation, but it must be pointed out at this time that the microscopic and electronmicroscopic changes observed in this patient were similar to those observed by us in cases of typical lipoid nephrosis in childhood, and show a similar reversal to normal with treatment [23]; moreover, at the time of writing this paper the patient has no clinical evidence of renal disease.

Among the causes of the nephrotic syndrome, the most difficult to differentiate one from the other are membranous glomerulonephritis and lipoid nephrosis. Many pediatricians consider that almost all cases of "nephrosis" in childhood are due to lipoid nephrosis, while most physicians who see adults with the nephrotic syndrome diagnose glomerulonephritis. There is no agreement among pathologists about the histology of these conditions or about the meaning of the term nephrosis, which is interpreted by some as any degenerative disease of the tubules. These difficulties, of both semantics and interpretation, have resulted in the present confusion so obvious in the medical literature. The following facts have added to this confusion:

Contrary to widely held opinions, there is no definite correlation between the clinical findings of hypertension, azotemia and hematuria on the one hand, and the degree of damage to the glomerulus on the other. This statement is particularly pertinent to the patient under discussion here. Azotemia was severe, and hypertension moderate, yet the glomerular altera-

tions could be demonstrated only by electronmicroscopy. Moreover, concomitant with the disappearance of the edema the nonprotein nitrogen returned to normal, and the blood pressure is now normal. Similar observations have been recorded by us in other nephrotic patients.[16]

Until recently, lipoid nephrosis could be diagnosed only retrospectively, by demonstrating that the patient was free of renal disease many years after the original illness. The kidneys of such patients have rarely been available for study by the pediatrician or physician who originally treated the patient for his nephrotic syndrome. Now, the use of percutaneous renal biopsy enables us to study seriatim the kidneys of these patients, and especially to make an evaluation of the state of their glomeruli when the patients are first swollen with edema.

We have made a diagnosis of "lipoid nephrosis" in this patient. Are we able to predict that he will not develop membranous glomerulonephritis and renal failure in the future? A definite answer cannot be given at the present time. Lipoid nephrosis is more commonly seen in children than in adults, and it is well known among pediatricians that many of these children may recover completely. In adults, on the other hand, lipoid nephrosis has been considered to be a very rare cause of the nephrotic syndrome.[24] Almost all adults with the nephrotic syndrome are said to develop renal failure, but in our experience some adults who have lipoid nephrosis may recover from the nephrotic syndrome without any evidence of persistent renal damage. Several questions must be asked: Are lipoid nephrosis and membranous glomerulonephritis different diseases, or are they, as Ellis[25] believed, indistinguishable from one another? Do they represent the response of the kidney to different stimuli, or do the glomerular basement membranes of the infant and child react to the same stimuli in a manner different from that of adults? Does lipoid nephrosis develop into membranous glomerulonephritis? If this does occur, is it the result of complicating local factors such as disturbed circulation within the glomerular capillaries, or the result of continuing proteinuria? Serial studies of patients, using electronmicroscopy in addition to routine and special histologic technics, may eventually provide an answer to these questions, since observations made by other authors have not. From his study of kidney tissue obtained post mortem, Allen concluded that the glomerular basement membrane was thickened in all patients with the nephrotic syndrome, whatever the cause. Moreover, he asserted that this alteration of the glomerular basement membrane was such as to be easily demonstrable with hematoxylin and eosin stains alone.[26] Ehrich[27] and Bell,[28] on the other hand, have pointed out that special stains, such as the periodic acid-Schiff, Mallory or Ritter and Oleson's acid and periodate polysaccharide, are necessary to demonstrate the abnormalities in the glomerular basement membrane, which they believe to be universally present. We have reported previously that even with these special staining technics the glomerular basement membrane appears to be

normal in the kidneys of some nephrotic patients which were studied by biopsy technics.

The controversy about the thickening of the glomerular basement membrane, discussed above, is due to the fact that the limits of resolution of the light microscope are such that the lamina fenestrata, the basement membrane and the pedicels cannot be separated clearly from one another, particularly when routine 6 micron sections are studied and even when sections are cut at 1 micron. Any increased staining of "basement membrane" by light microscopy may be due to thickening of the true lamina densa or of the lamina fenestrata, or to alterations in the podocytes, in particular the replacement of the pedicels by a continuous layer of epithelial cytoplasm or collapse of trabeculae onto the lamina densa. It is for this reason that electron-microscopy is becoming a necessary tool for the pathologic evaluation of many renal diseases, and particularly for the study of the early lesions seen in renal biopsy specimens.

The observations on the microanatomy of the kidney reported here and elsewhere indicate that the podocyte may play a role in the ultrafiltration of plasma, previously attributed by some to the endothelial cells and basement membrane. This relationship was discussed in detail by Hall,[5] who has demonstrated that the epithelial cells of the tubules and the podocytes develop embryologically from the same cells and undergo a similar but not identical differentiation.[15] The data available at the present time do not yet provide a clear answer to the mechanism of proteinuria in the nephrotic syndrome. From light microscopic studies the tubules are known to be damaged, and as electronmicroscopy has now shown that there are abnormalities in the podocytes in lipoid nephrosis, we may speculate that the tubular cells and podocytes act as a functional unit in relation to filtration and reabsorption of protein. It may be that a single noxious stimulus acts simultaneously on these embryologically related cells to produce both the proteinuria and the glomerular and tubular changes seen in lipoid nephrosis.

Addendum

Since this paper was written the patient has been followed for a further period of ten months. He remains in excellent health, his renal function is normal, and the biochemical findings in his serum are normal. In eight 24-hour specimens of urine examined since November, 1957, no protein has been found. His urinary sediment is normal.

Acknowledgments

We wish to thank Professor John Marbarger, Director of Research in the Aeromedical and Physical Environment Laboratory, for his kind interest in our work and for his help; our dietitian, Miss Rosemary Gleason, for preparing the diets; and Dr. R. E. Bedard, of Kankakee, Illinois, for referring this patient to us and for his records on the patient's early history.

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Summario in Interlingua

Inter le causas del syndrome nephrotic, glomerulonephritis membranose e nephrosis lipoide es le plus difficile a differentiar le un ab le altere. Multe pediatros opina que quasi omne casos de "nephrosis" in juveniles resulta de nephrosis lipoide, durante que le majoritate del medicos qui vide un adulto con le syndrome nephrotic presenta le diagnose de glomerulonephritis. Il existe nulle accordo inter le pathologos quanto al histologia de iste conditiones o quanto al signification del termino "nephrosis," le qual es interpretate per certe autores como designation pro omne morbo degenerative del tubulos. Iste difficultates—semantic e interpretative—ha resultate in le presente confusion, que es si obvie in le litteratura medical.

Usque recentemente, nephrosis lipoide poteva esser diagnosticate solmente in retrospecto, per demonstrar que le patiente esseva libere de morbo renal multe annos post su maladia original. Le renes de tal patientes ha rarmente essite disponibile al studio per le pediatro o medico qui tractava originalmente lor syndrome nephrotic. Hodie, le uso de percutanee biopsias renal rende possibile a nos effectuar studios serial del renes de tal patientes e specialmente evalutar le stato de lor glomerulos quando illes exhibi le prime signos de edema.

In 11 patientes, degeneration e alterationes de grassia esseva observate in le tubulos, sed le observation per microscopia a lumine permitteva le conclusion que le glomerulos esseva intra le limites normal, mesmo post le application de tincturas special. Le etates del patientes variava inter 15 e 83 annos. Omnes qui esseva tractate con ACTH o hormones adreno-corticosteroide respondeva con un diurese excellente. Quando evalutationes esseva effectuate ab le puncto de vista clinic e biochimic e per medio de biopsias renal in serie, nulle signo de progressive morbo renal esseva trovate in le curso de periodos de observation de usque a tres e medie annos.

Studios de microscopia electronic esseva initiate con le objectivo de definir plus precisemente le pathologia del glomerulos de ille patientes. Usque hodie, studios individual ha essite facite in quatro patientes e studios serial in tres alteres. In le presente articulo nos reporta in detalio le observationes clinic, histologic, e de microscopia electronic in un patiente in qui lesiones glomerular esseva demonstrabile solmente per medio del microscopio electronic. Iste lesiones esseva reducite al stato normal per un therapia a prednisona. Al tempore del prime biopsia le patiente esseva multo edematose. Pro obtener observationes representative, septe glomerulos esseva examinate. Alterationes de character similar esseva constatate in omnes. Le alterationes le plus frappante esseva vidite in le podocytos. Lor pedicellos habeva disparite e habeva essite reimplaciate per un strato continue de cytoplasma epithelial de spissitate irregular. Iste cytoplasma epithelial anormal esseva clarmente distinguite ab le lamina dense per differentias de affinitate pro osmium.

Si le alterationes observate in le podocytos esseva frappante, nulle anormalitate esseva detegite in le membrana basal del glomerulos o in le cellulas endothelial. Le membrana basal del glomerulos (lamina dense) esseva de spissitate normal. Illo esseva homogenee e non structurate. Su densitate e su osmiophilia esseva satis uniforme. Esseva trovate numeros normal de cellulas endothelial. Lor cytoplasma e lor nucleos pareva esser normal, e le mesmo valeva pro le lamina fenestrate.

Le secunde biopsia esseva effectuate post que le patiente habeva recipite un curso de 31 dies de doses diurne de 40 mg de prednisona. Ille habeva perdite su edema completemente. Solmente grados minimal de anormalitate esseva vidite in le podocytos. Esseva observate clarmente que le pedicellos coperiva le lamina dense de quasi omne le ansas capillar. Le majoritate del pedicellos esseva normal, ben que in certe casos illos non esseva distinctemente separate le unes ab le alteres al puncto adjacente al lamina dense.

Quando le tertie biopsia esseva effectuate, le patiente esseva ancora sub tractamento a prednisona in doses diurne de 25 mg. Su stato de sanitate esseva excellente. Le apparentia del glomerulos esseva nunc completemente normal. Le podocytos e lor processos esseva etiam normal. In particular, lor pedicellos jaceva regularmente al longo del lamina dense e esseva distinctemente separate le unes ab le alteres al puncto de lor insertion in le membrana basal.

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SOME RECENT DEVELOPMENTS PERTAINING TO PANCREATITIS *

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SINCE the second century of the Christian era, when the pancreas was apparently considered by Galen to be a mechanical cushion for the stomach,[1] knowledge regarding the structure and functions of this organ in both health and disease has advanced considerably. This knowledge has been derived from experimental as well as clinical and pathologic observations, and, although significant gaps remain, it is encouraging that new developments continue.

It is intended to review here some of the recent developments pertaining to pancreatitis, first mentioning some observations regarding the natural history of the disease and then considering several interesting, if poorly understood, biochemical abnormalities sometimes associated with pancreatitis, study of which may point the way eventually to a better understanding of the disease.

PANCREATITIS AT THE MAYO CLINIC IN 1956

It may be of general interest to note first some observations pertaining to the incidence of pancreatitis and sequelae at the Mayo Clinic in a recent representative year, 1956. In that year 125 patients with pancreatitis were seen at the clinic. Of this number 80 (64%) appeared to have primary pancreatitis; 75 of these 80 (60% of the entire group) had chronic relapsing pancreatitis; only five (4%) had primary acute pancreatitis (no historical or other evidence of previous attacks). The annual frequency with which chronic relapsing pancreatitis has been recognized at the clinic has increased roughly fivefold in the last decade, since the classic descriptions of the syndrome by Comfort, Gambill and Baggenstoss.[2, 3]

The over-all sex incidence in the 125 cases was 2.7 males to 1 female. Among the 75 patients with chronic relapsing pancreatitis, males predominated 4.2 to 1. The ages of the 125 patients ranged from six to 75 years, and the mean age was 49 years. For the 75 patients with relapsing pancreatitis the age range was the same, and the mean age was 45 years.

Among the 75 patients with chronic relapsing pancreatitis there were 71 without associated disease of the biliary tract; in two there were soft pig-

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mentary deposits in the common bile duct which were probably secondary to the obstructing process (pancreatitis) in the head of the pancreas. One patient had stones in the gall-bladder, and one other patient had a single stone in the gall-bladder with slight thickening of that organ.

In four (5%) of the 75 cases of chronic relapsing pancreatitis the condition was either painless or essentially so. In 10 (13%) it was of the hereditary type. In two cases hyperlipemia was associated, but in most instances the serum was not turbid, and determinations of serum lipid were not made. Values for serum calcium were slightly high in one of the 20 patients so studied.

Thirty-eight (51%) of the 75 patients with chronic relapsing pancreatitis were without any of the sequelae of the disease. In 18 of these 38 the presence of pancreatitis was proved at operation. In the other 20 the history was characteristic of chronic relapsing pancreatitis, and 10 of these 20 exhibited elevated values for serum amylase or lipase or both at the time of examination at the clinic.

Among the 37 patients (49%) with chronic relapsing pancreatitis and sequelae there were six with the full triad of diabetes mellitus, calcification and steatorrhea. Thirteen of the 37 had only calcification of the pancreas, two had only steatorrhea, three had only pseudocyst, and one had only diabetes. Four patients had calcification and diabetes; one, calcification and steatorrhea; two, calcification and pseudocyst; two others had calcification, pseudocyst and diabetes, and one of these two also had an abscess of the pancreas. Only one patient in the group had diabetes and steatorrhea without pancreatic calcification. Two patients with chronic relapsing pancreatitis had portal hypertension secondary to thrombosis as a result of the pancreatitis: one of these had thrombosis of the splenic vein with variceal bleeding as well as pancreatic calcification and steatorrhea; the other patient had portal venous thrombosis and also chylous ascites.

In four of the five patients with primary acute pancreatitis the diagnosis was confirmed at operation. The diagnosis rested on clinical evidence alone in the fifth case, where hyperlipemia was associated.

In 45 cases (36%) the pancreatitis appeared to be secondary to other processes; in 35 of these it was secondary to calculous disease of the biliary tract—that is, acute, subacute or chronic cholecystitis with stones in the gall-bladder and frequently in the common bile duct as well. Most often in these 35 cases the pancreatitis was detected at operation, was slight to moderate in degree, and was localized. Pancreatitis occurred with, and was probably secondary to, carcinoma of the head of the pancreas in three cases, and carcinoma of the papilla of Vater in one case. In two instances the pancreatitis was considered to be secondary to stricture of the common bile duct, with associated stone in the common duct in one of these. In one patient the pancreatitis appeared to be secondary to a penetrating duodenal ulcer. In three instances pancreatitis occurred in the immediate postoperative

period; in one it occurred after cholecystectomy and choledochostomy for gall-stones, and in another case after subtotal gastrectomy. Acute pancreatitis (unsuspected clinically) was found in the third case at necropsy one week following transurethral prostatic resection and bilateral orchiectomy for carcinoma of the prostate gland; oliguria had been present for five days ante mortem.

Painless Pancreatitis

Although clinically the hallmark of chronic pancreatitis is recurrent bouts of severe upper abdominal pain lasting for days or longer, and followed by epigastric tenderness for a day or so, for some years it has been recognized that occasionally pancreatitis may be painless, or essentially so.[3-13] This feature has been emphasized recently by Bartholomew and Comfort,[10] who described 10 cases of relatively painless chronic pancreatitis. The incidence of chronic pancreatitis without pain would appear to be low; as noted above, in four (5%) of the 75 cases of chronic relapsing pancreatitis encountered at the clinic in 1956, the condition was essentially painless. The diagnosis is to be suspected when, without the patient's having experienced abdominal pain, sufficient pancreatic destruction has developed that he has the sequelae of chronic pancreatitis: pancreatic calcification, diabetes mellitus and steatorrhea. All these may coexist, or they may occur in various combinations. Infrequently, painless jaundice may be found at operation to have resulted from pancreatitic obstruction of the common bile duct.

The following case is an example of painless chronic pancreatitis.

Case 1. A 53 year old white man first came to the clinic on July 13, 1956, complaining of having had low back pain of static type for the preceding 25 years. He also mentioned the occasional occurrence of mild epigastric and substernal burning distress for the four or five years prior to examination, particularly when reclining.

Physical examination disclosed no significant abnormalities aside from moderate obesity. The routine laboratory studies of blood and urine gave normal results. The values for serum bilirubin were normal, as were values for serum amylase and lipase. The fasting blood sugar was 127 mg. per 100 ml. On roentgenologic study of the stomach a diaphragmatic hernia with 3 inches of stomach above the diaphragm was discovered. Roentgenograms of the spinal column showed lumbar scoliosis and hypertrophic changes, and unexpectedly also revealed calcification in the head of the pancreas (figure 1*a*).

It was felt that the diaphragmatic hernia accounted for the patient's epigastric and substernal distress, and that the degenerative changes of the spinal column were responsible for the low back pain. The diagnosis of painless chronic pancreatitis with pancreatic calcification and mild diabetes mellitus was made also. The patient was treated conservatively for the osteoarthritis and diaphragmatic hernia. Reduction in weight was advised.

The patient returned to the clinic on August 19, 1957, because he had passed two to four bulky, foul-smelling, fatty-appearing stools daily for the preceding six months; the steatorrheal diarrhea had been worse for the two months just prior to his return. He had also noted excessive thirst and some increase in urinary frequency. Although his appetite had remained good, he had lost 25 pounds, largely through dieting.

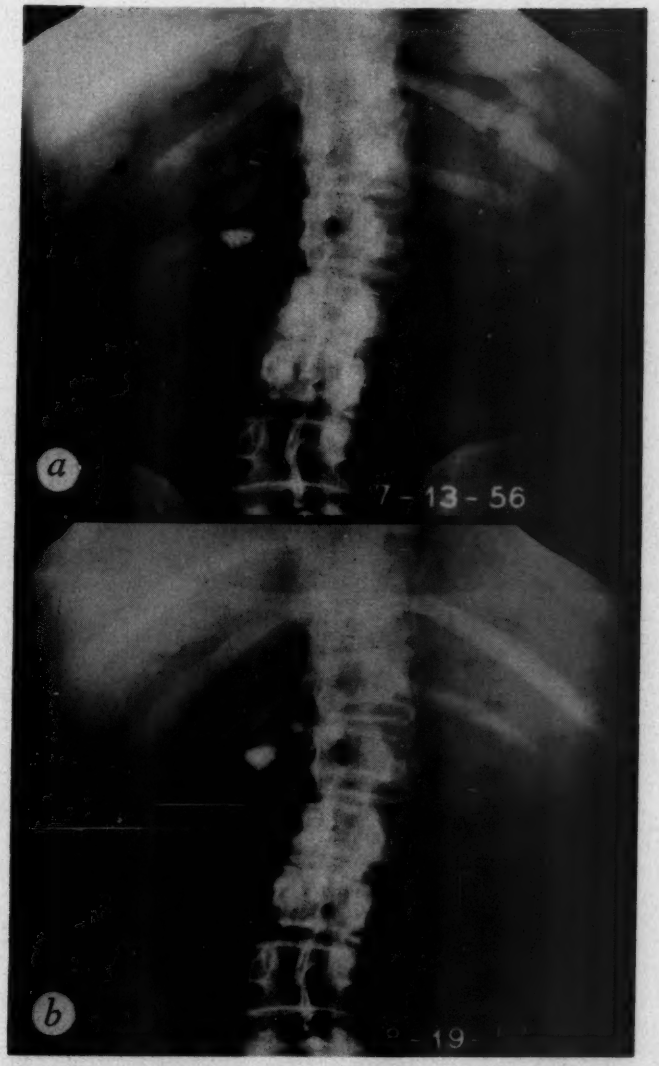

FIG. 1. *Case 1.* Pancreatic calcification. *a.* July, 1956. *b.* August, 1957. Note the increase in size and number of calcific deposits in this 13-month period.

Again physical examination disclosed no significant abnormalities. Routine urinalysis disclosed marked glycosuria. The fasting blood sugar measured 323 mg. per 100 ml. Values for serum amylase, lipase, bilirubin and calcium were normal. Roentgenograms of the pancreas disclosed more extensive pancreatic calcification than had been evident 13 months before (figure 1*b*). Cholecystography showed a normally functioning gall-bladder. Again the diaphragmatic hernia was demon-

strable, though apparently slightly smaller than at the time of the previous examination. Roentgenologic examination of the colon and terminal ileum revealed only a few colonic diverticula. Microscopic examination of a stool disclosed oil, and analysis of a 24-hour specimen of stool showed that the fat comprised 62.6% of the dry weight (40 gm. in 24 hours), and that 2.6 gm. of nitrogen was passed per day in the feces.

The diagnosis was painless chronic pancreatitis with the triad of sequelae. The patient was treated with a diet qualitatively modified for the diabetes and 36 units of lente insulin each morning. Pancreatin was given with the meals.

The patient gave no history of pain characteristic of chronic pancreatitis; the diagnosis was established when pancreatic calcification was detected in roentgenograms made for another purpose. Diabetes mellitus and steatorrhea completed the triad of sequelae.

The diagnosis of painless pancreatitis should not be abused. It is indefensible (though not necessarily incorrect) for the clinician to attribute mild and indefinite abdominal symptoms to painless pancreatitis in the absence of demonstrable sequelae of chronic pancreatitis; the diagnosis rests on demonstration of these sequelae or on surgical or histologic proof.

Recent evidence suggests that the acute or subacute edematous (interstitial) form of pancreatitis also may occur without abdominal pain. Evans,[14, 15] in a review of the 25 cases of this condition at necropsy at the clinic in the 35-year period from 1921 through 1955, was unable to discover any indication that abdominal pain had occurred in 15 (60%). All 25 patients had died of conditions other than the pancreatitis. Although the disadvantages to such retrospective appraisal of clinical histories are obvious, it nevertheless appears that any abdominal pain which these 15 patients may have experienced was probably of such trivial nature that it went unremarked. Such observations suggest that acute edematous pancreatitis may occur more frequently than is suspected, and that it may undergo complete resolution without the cognizance of either patient or physician. How often such episodes progress to complete recovery and how often acute edematous pancreatitis may eventuate in chronic pancreatitis are unknown at present.

Hereditary Pancreatitis

The unusual prevalence of pancreatitis in some families is a rather spectacular phenomenon, first described in 1952 by Comfort and Steinberg;[16] since then several other kindreds have been observed at the clinic.[17, 18] The genetic observations to the present indicate that in these families pancreatitis is inherited as a nonsex-linked mendelian dominant trait; whether the phenomenon of poor penetrance is involved is still not clear.

One of the most remarkable features of hereditary pancreatitis has been the early age at onset, attacks beginning in most cases in childhood or early adult life. In the kindred most closely studied and most extensively involved to date (K. family),[17] the average age at onset was 12 years, whereas in a series of 29 unrelated patients with nonhereditary pancreatitis[3] it was

38 years. This onset in childhood has been observed frequently in persons with hereditary pancreatitis but has been unusual in the nonhereditary form of the disease, in which attacks most often begin in the fourth decade of life. Thus one should suspect the hereditary form of the disease if the patient is a child or young adult, or if the attacks date back to childhood. Other clinical features which appear to be peculiar to the hereditary (as opposed to the nonhereditary) form of pancreatitis are the predominance in females, lack of associated gall-stones, and a tendency for the pancreatic calcification to appear as calculi in the larger pancreatic ducts. So far, alcoholism and hyperlipemia have been observed infrequently in patients with hereditary pancreatitis. With regard to most of the other clinical features, hereditary and nonhereditary pancreatitis are alike.

In case 2 the pancreatitis was probably of the hereditary type.

Case 2. A 21 year old white woman came to the clinic on May 29, 1956, with the chief complaints of anemia and four episodes of melena since the age of nine years. As far back as she could recall, she had passed oil per rectum, especially following ingestion of fatty foods. At the age of nine years she had begun to experience recurrent episodes of moderately severe epigastric pain which would cause her to double over and which lasted from a few minutes to eight hours. These had occasionally required opiate for relief, and had been followed by epigastric tenderness for a day or so.

Physical examination was essentially negative except for slight epigastric tenderness. The laboratory studies revealed moderate anemia of the hypochromic type. Values for serum bilirubin, amylase and lipase were all normal, and the fasting blood sugar measured 107 mg. per 100 ml. Roentgenograms of the abdomen showed extensive calcification of the pancreas (figure 2). Roentgenologic studies of the esophagus, stomach, duodenum and colon otherwise showed nothing of significance.

The source for the recurrent upper gastrointestinal bleeding was not apparent, and the advised abdominal surgical exploration was performed on June 11, 1956. There was evidence of previously developed thrombosis of the splenic vein, very likely secondary to chronic pancreatitis, with development of numerous collateral veins where the splenic vein would normally have been. Large, dilated veins were present over the stomach, including the gastroepiploic veins along the greater curvature of the stomach. The pancreas was fibrotic and extensively calcified, and numerous calculi were removed from the main pancreatic duct in the region of the body of the pancreas. The tail of the pancreas and the spleen, which was enlarged to three times normal size, were removed. T-tube decompression of the pancreatic ductal system was maintained for some months thereafter, and the patient has done well since the operation; she has not required insulin or, if she avoids ingestion of fatty foods, pancreatin.

Familial History: At the time this patient was under our observation her brother, aged 27 years, was hospitalized elsewhere with an acute exacerbation of chronic pancreatitis, associated with fever and pseudocyst formation. He had had chronic pancreatitis for 10 years. Another brother, aged 34 years, had been troubled with characteristic, prolonged attacks of severe upper abdominal pain since the age of 15 years; although roentgenograms of the pancreatic region revealed no calcification in 1956, this brother's description of his attacks of pain leaves little doubt as to the diagnosis. The father of these three persons has been troubled with recurrent abdominal pains and "acid indigestion" for many years.

The onset of attacks in childhood suggests that the patient (case 2) has the hereditary form of pancreatitis. The apparent involvement of two brothers corroborates this suspicion. Splenic or mesenteric venous thrombosis secondary to pancreatitis has been observed occasionally in other

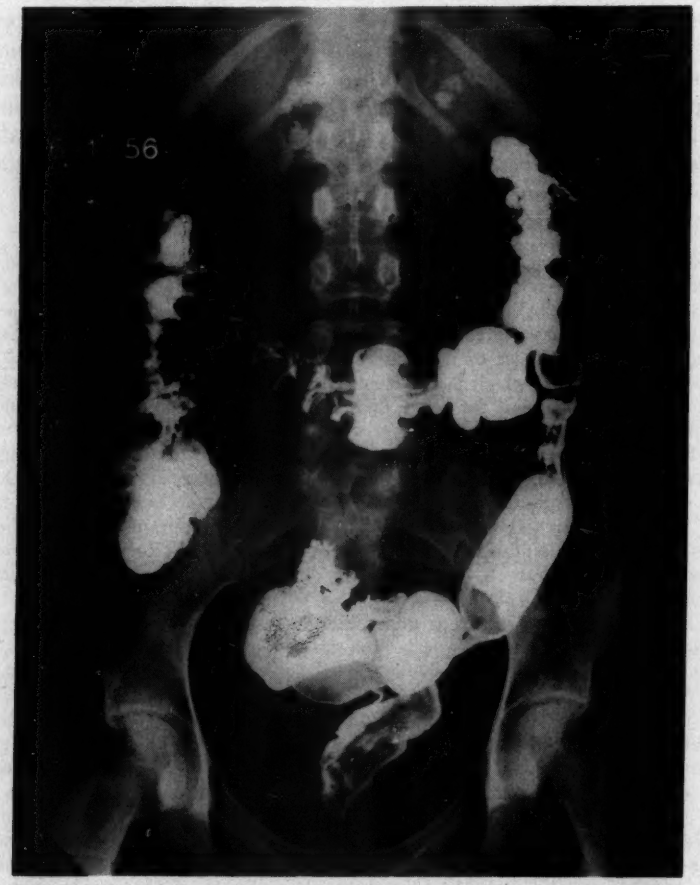

FIG. 2. *Case 2.* Extensive intraductal pancreatic calculi visible in roentgenogram of colon.

patients, and the consequent variceal bleeding is one of the less frequent causes for upper gastrointestinal hemorrhage.

It seems likely that not all cases of pancreatitis in childhood are of the hereditary variety. Collett and Kennedy [19] and Poulsen [20] have reported two cases of pancreatitis in children, in each of which a single sibling was possibly involved; hyperlipemia coexisted in these cases. Dobbs [21] and others [22–24] have reported instances of pancreatitis in children and referred

to previous such reports; with the exception of the patient studied by Stickler and Yonemoto,[24] the familial histories evidently were not revealing in these cases, and in some instances mumps, roundworms and trauma have been implicated as probable etiologic factors. In recent years my associates and I have occasionally encountered pancreatitis in children without a history of similar involvement of other members of the family.

Amino Acid Abnormalities in Pancreatitis

The inheritance of pancreatitis in accordance with mendelian laws in some families and the frequent appearance of the disease in childhood in those affected suggested that such persons might have inherited some predisposing abnormality, perhaps of a biochemical or metabolic nature, and prompted quantitative study of amino acids in the blood and urine of persons with pancreatitis.[25] Microbiologic assays were carried out for the apparent free and total forms of 14 amino acids in two groups: the first group was composed of seven persons with hereditary pancreatitis and four of their blood relatives apparently without the disease; 11 persons with proved chronic pancreatitis of the nonhereditary type comprised the second group. Certain quantitative abnormalities of the amino acids in serum and urine were obtained for both groups studied, but the most impressive abnormality was excessive excretion of lysine by most of those in the hereditary group, including a blood relative seemingly without pancreatitis from each of three (unrelated) kindreds.[18, 25]

Subsequent studies [26] have confirmed the original observations (figure 3). Amino-aciduria characterized principally by excessive excretion of lysine has been rather largely confined to the hereditary group and appears to be familial, persistent and only slightly variable on successive days. In one case the amino-aciduria was even more marked when studied a year after the initial determinations. This latter patient and two of her daughters, aged 20 years and six years, respectively, all with the hereditary form of chronic relapsing pancreatitis, as previously reported (pedigree numbers K-II-7, K-IV-7 and K-IV-13),[17] excreted large amounts of lysine in the urine. It is of interest that the mother and the 20 year old daughter exhibited marked lysinuria which was part of a more general amino-aciduria, and that lysinuria was detectable as early as the age of six years. Excretion of more than 2 gm. of lysine per day in the urine, three fourths of it as the free form, seems to be a significant abnormality.

The basis for the observed quantitative abnormalities of amino acids is not known. It seems probable that the amino-aciduria (lysinuria) in the patients with hereditary pancreatitis and their blood relatives results from some inherited biochemical abnormality. However, whether this abnormality has to do with intermediary protein metabolism or whether it may stem from deficiency of some enzyme concerned with reabsorption of lysine by the proximal convoluted tubule of the kidney is not known at present.

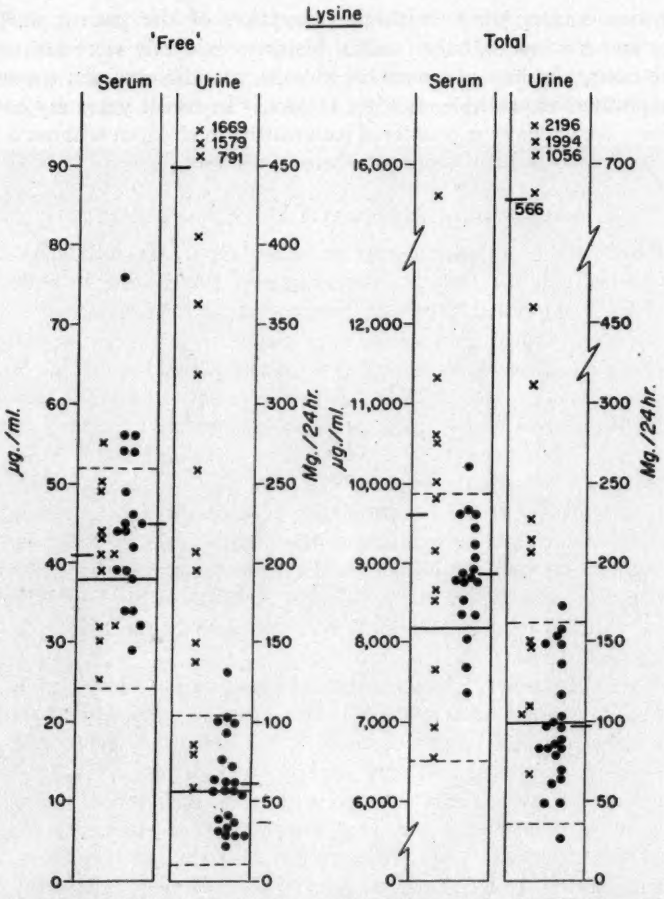

FIG. 3. Fasting values for lysine in serum and the quantity in 24-hour specimens of urine in persons in hereditary (×) and nonhereditary (●) pancreatitis groups. The solid line extending entirely across each column represents the normal mean. The broken lines indicate the upper and lower limits of normal based on ± 2 S.D. The means for the two pancreatitis groups are designated by the shorter, solid lines.

It is not yet established that the observed amino acid abnormalities have any etiologic relationship to the pancreatitis, but the present evidence suggests that these abnormalities have not resulted from the pancreatitis. Further studies should help to clarify the basis for the observed quantitative abnormalities of amino acids and their significance.

HYPERPARATHYROIDISM AND PANCREATITIS

In 1923 Dawson and Struthers [27] described a case of hyperparathyroidism where there were widespread calcific deposits in the form of fine granules

throughout the body, including ". . . all the internal organs." In 1939 a similar case was reported by Hanes [28] and another by Oliver; [29] in the reports of these three cases there were no specific allusions to pancreatic calcification or pancreatitis. In 1940 Smith and Cooke [30] described a patient with hyperparathyroidism and extensive nephrocalcinosis in whom the pancreas was swollen, partially necrotic, and the seat of diffuse calcinosis. Since that time there have been reports [31-40] of 13 other cases of hyperparathyroidism with associated pancreatitis, pancreatic calcification, or both, and the frequency of such reports seems to be increasing.*

Case 3 is another instance where hyperparathyroidism and chronic relapsing pancreatitis coexisted.

Case 3. A 41 year old white man, first examined at the clinic on August 22, 1955, complained of having had recurrent "kidney stones" since 1943, in which year he had passed a stone spontaneously in the urine. Since that time he had experienced attacks of bilateral flank pain, had passed stones spontaneously on at least six occasions, and had undergone surgical removal elsewhere of four other calculi from the ureters. In 1949 he noted the onset of recurrent attacks of severe, deep, aching pain in the lower retrosternal and interscapular regions, referred to the epigastrium and left flank. In 1950 one such attack of pain, which lasted three days and was associated with fever and vomiting, eventuated in surgical exploration of the abdomen. The patient was later told that the "pancreas had probably ruptured." Nine weeks later he experienced painless jaundice for about three months. In 1951 diabetes mellitus was discovered, and since that time the patient had required 15 units of isophane (NPH) insulin and qualitative modification of his diet to control this condition. In November, 1952, the concentration of serum calcium determined elsewhere was 13.2 mg. per 100 ml., and that of serum phosphate, 2.9 mg. From 1950 to 1955 the patient had experienced recurrent bouts of lumbar pain, apparently due to renal calculi. In January, 1955, upper abdominal, lower retrosternal and interscapular pain had recurred almost weekly; the pain usually was associated with vomiting and required hypodermic injection of opiates for relief. This pain had often awakened the patient from sleep, and was worse after ingestion of food. He had lost 30 pounds since 1952. From 1943 to 1955 he had drunk a pint of whiskey daily, and since that time he had consumed a pint of whiskey three times a week on the average.

The familial history was of note in that the father was said to have had diabetes mellitus.

On examination at the clinic there was no fever. The patient was 68 inches tall and weighed 110 pounds. No diabetic retinopathy was observable. A palpable epigastric mass was considered to be an enlarged pancreas.

Urinalyses repeatedly showed slight glycosuria, moderate albuminuria and a moderate number of erythrocytes and leukocytes in the centrifuged sediment. The blood hemoglobin measured 12.4 gm. per 100 ml.; the leukocyte count was 11,800

* The exact number of such case reports is somewhat indeterminate at present. In Jackson's [37] interesting family, in which two brothers had pancreatitis and hyperparathyroidism, their mother (with hyperparathyroidism) may also have had chronic relapsing pancreatitis. There are, in addition, similar cases that apparently have been discovered but have not been reported yet.[41, 42] In recent years we have encountered at the clinic one other patient with definite chronic relapsing pancreatitis and hypercalcemia, but the basis for the latter abnormality is as yet undetermined.

Since submission of this manuscript yet another case of coexistent pancreatitis and hyperparathyroidism has been noted. (Hoar, C. S. Jr., and Gorlin, R.: Hyperthyroidism and acute pancreatitis, New England J. Med. **258**: 1052, 1958.)

per cubic millimeter, and the value for fasting blood sugar was 195 mg. per 100 ml. The serum calcium measured 11.3 mg. per 100 ml. on one occasion and 11.5 mg. on another; the corresponding values for serum phosphate were 2.8 and 3.2 mg. per 100 ml. The serum alkaline phosphatase measured 16.8 King and Armstrong units. Roentgenograms of the chest showed nothing significant; those of the hands disclosed only slight osteoporosis. Dental roentgenograms showed apparent thinning of the lamina dura. Cholecystography revealed a nonfunctioning gall-bladder and extensive calcification of the pancreas. A plain roentgenogram of the kidneys, ureters and bladder and excretory urograms showed, in addition to the multiple areas of pancreatic calcification, multiple stone shadows in the left renal area and no function of

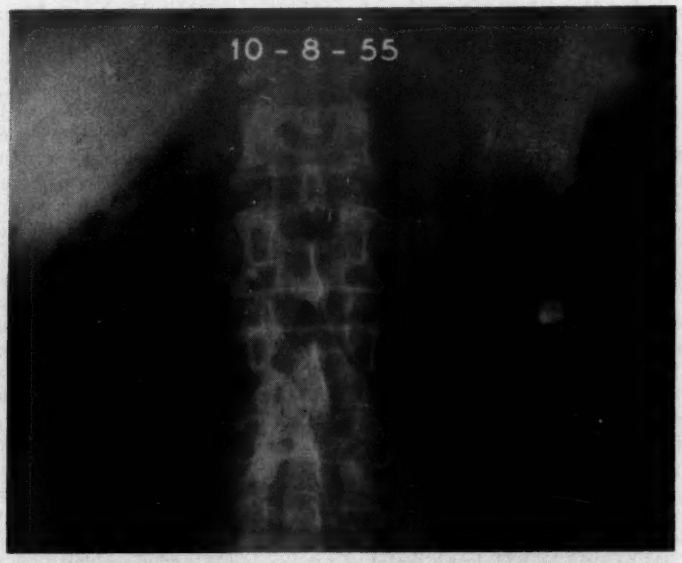

FIG. 4. *Case 3.* Note extensive pancreatic calcification as well as multiple shadows of stones in the left kidney.

the right kidney (figure 4). By means of cystoscopy and retrograde pyelography a 3 cm. calculus was demonstrated above the right ureteral orifice, as were a left ureteral calculus and left hydronephrosis. While ingesting a low calcium (Aub) diet the patient excreted an average of only 73 mg. of calcium daily in the urine over a three-day period.

The patient was considered to have chronic relapsing pancreatitis with diabetes mellitus and pancreatic calcification. The stones in the ureters and left kidney were regarded as probably secondary to hyperparathyroidism, despite the lack of hypercalciuria. From 25 to 30 units of lente insulin each morning and appropriate qualitative modification of the diet were required to control the moderate diabetes.

At surgical exploration of the parathyroid glands on September 10, 1955, a parathyroid adenoma was removed which measured 1.5 cm. in diameter and was located in the usual position of the left superior gland. The remaining three parathyroid glands appeared to be normal. Histologic examination of the parathyroid adenoma, which weighed 1,230 mg., revealed an adenoma of the chief cell type

(figure 5). On November 9 the value for serum calcium was 10.0 mg. per 100 ml., and that for phosphate, 3.7 mg. On November 23 the serum calcium measured 9.1, phosphate 3.3, mg. per 100 ml.

Bilateral ureterolithotomy was carried out on September 26, 1955. Soft accumulations of calcareous material were removed from the left ureter, and multiple small stones from the right ureter. A postoperative stricture of the lower right ureter was encountered at that operation and was intubated. On November 14, 1955, left renal pelviolithotomy was performed, with removal of a large, friable stone from the lower calyx and innumerable sandy particles from the left renal pelvis. Chemical examination of the stone revealed calcium carbonate and calcium phosphate.

FIG. 5. *Case 3.* Chief cell adenoma of left superior parathyroid gland removed September 10, 1955 (hematoxylin and eosin; × 175).

The patient experienced two attacks of mild epigastric and substernal pain, probably representing exacerbations of the chronic pancreatitis, shortly after parathyroidectomy. The one began on October 28, 1955, and persisted for four days; the other, which was similar, began on December 5, 1955.

Since his three operations the patient has felt "better than in 14 years," having experienced much less frequent and severe attacks of epigastric pain. He did have what was interpreted as a severe attack of pancreatitis in May, 1956, and a few mild, brief attacks in the ensuing eight months. However, he had gained 25 pounds and had not had subsequent urinary symptoms or formation of renal stones up to January 20, 1958.

To date then, there are at least 15 cases where hyperparathyroidism and pancreatitis (or pancreatic calcifications) have been reported to coexist. Six of the 15 patients were women; the ages ranged from 27 to 68 years at the time of the reports. Three were Caucasian and two were Negroes; the race of 10 patients was not stated. The parathyroid lesion in 11 cases was adenoma, in two wasserhelle hyperplasia, in one carcinoma, and in one

"tumor." The values for serum calcium were elevated in each of the 13 patients when such analyses had been performed before operation or death.

The nature of the pancreatic lesion was not always clear in these reports. In eight of the 15 cases there were pancreatic "calcifications" or "calculi"; in the reports of three of the eight cases where calcific deposits were found in the pancreas, there was no specific mention of pancreatitis, whereas in the other five both pancreatitis and areas of pancreatic calcification were noted. Thus pancreatitis, either acute or chronic, or both, existed in 12 of the 15 cases, and in seven of these 12 cases pancreatitis existed apparently without pancreatic calcification. There were calcific deposits in the kidneys in nine of the 15 cases; in six of the nine these were renal calculi, whereas in three, nephrocalcinosis existed. In six cases calcification had appeared in both the pancreas and the kidneys, whereas in three cases there were deposits of calcium in the kidneys without reference to any in the pancreas, and in two instances pancreatic calcification existed without any in the kidneys.

The duration of the pancreatitis or pancreatic calcification and the duration of the hyperparathyroidism appeared uncertain in most of these 15 cases. Whereas in five of the 15 cases hyperparathyroidism may well have preceded the onset of the pancreatic lesions, in one case pancreatitis conceivably antedated the hyperparathyroidism. The temporal relationship was quite indefinite in the other nine cases.

Whether hyperparathyroidism and coexistent pancreatitis represent more than coincidental association in these few cases is not known at present. It has been suggested both that the hyperparathyroidism may have led to pancreatitis [37, 38] and that the pancreatitis and sequelae may have led to hyperparathyroidism.[39] In regard to the first suggestion, it is well recognized that a local milieu in the body which is alkaline—for example, the external pancreatic secretion—favors the precipitation of calcium salts. The hypercalcemia of hyperparathyroidism presumably also may favor calcific deposits within the pancreatic ductal system, for the concentration of calcium in human pancreatic juice normally approximates the concentration of diffusible ionic calcium in the plasma.[43-46] However, whether the concentration of calcium in human pancreatic juice is increased when hypercalcemia exists—that is, whether the calcium in the pancreatic juice is in equilibrium with the diffusible ionic calcium of the plasma—is not known. Moreover, information is lacking in regard to the calcium content of external pancreatic secretion in cases of pancreatitis. Tissue damage is also thought to favor calcific deposition. It is therefore a rather plausible suggestion that hyperparathyroidism may lead to calcific deposits in the pancreas, particularly in the pancreatic ductal system, where the pancreatic secretions are highly alkaline. It seems likely that pancreatic ductal obstruction by such calculi predisposes to chronic pancreatitis. Although at present this theory—that the pancreatitis is secondary to the hyperparathyroidism—cannot be disproved, it is pertinent to observe that in seven of the 15 cases where hyper-

parathyroidism and pancreatic disease coexisted the pancreatic lesion was apparently pancreatitis without detectable calcification.

It is somewhat more difficult to accept the second hypothesis—namely, that slight hypocalcemia associated with chronic pancreatitis and external pancreatic insufficiency may be the stimulus for formation and hyperfunctioning of a parathyroid adenoma. One might suppose that any such chronic hypocalcemic influence would affect all of the parathyroid glands equally, with resultant hyperplasia.

In two reported instances [33, 34] the pancreatitis appeared as a complication in the postoperative course after parathyroidectomy, and in another [38] of the 15 cases it seems likely that an episode of pancreatitis which had perhaps begun two months prior to parathyroidectomy underwent an exacerbation after the parathyroid operation. Again, whether this occurrence of pancreatitis shortly after an operation in an area some distance from the pancreas was more than coincidence is not clear; the pancreatitis need not have been causally related to the operation or to the metabolic consequences of parathyroidectomy.* In one of Cope's [38] cases, and in case 3 herein reported, the frequency and severity of episodes of pancreatitis decreased after removal of the parathyroid adenoma. Such improvement in only two cases, the short periods of postoperative observation, and the somewhat unpredictable course of chronic relapsing pancreatitis make it difficult to evaluate the question of whether parathyroidectomy has been responsible for the observed improvement. A number of other variables also complicate the evaluation; in case 3, for example, the patient had undergone urologic operations shortly after parathyroidectomy and also had curtailed his intake of alcohol during the postoperative period of improvement.

As Cope and associates [38] indicated, a practical point emerges from this occasionally observed coexistence of hyperparathyroidism and pancreatitis: one should be suspicious of serum calcium values which are higher than might be anticipated when the pancreatitis is active. As is well known, the concentration of serum calcium is often somewhat decreased during active pancreatitis; such lowering at that time may mask temporarily the hypercalcemia of hyperparathyroidism. Therefore, when one encounters in a patient with active pancreatitis concentrations of serum calcium which seem relatively high, considering the fact that the pancreatitis is active, it is well to think of the possibility of coexistent hyperparathyroidism and to recheck the serum calcium values later on, when the pancreatitis has become quiescent.

Although the significance of the coexistence of hyperparathyroidism and pancreatitis in the same person is not clear at present, it is well to be on the watch for such cases, for future observations should help to determine whether the relationship is more than a coincidental one. It is possible that future study of such patients will disclose an etiologic relationship.

* Pancreatitis has also occurred shortly after transurethral prostatectomy and after thyroidectomy in a few instances, basis uncertain.[14, 47–50, 50a] (Also see above.)

Pancreatitis with Achlorhydria

Although the pathogenesis of pancreatitis is imperfectly understood, numerous experimental and clinical observations point to the importance of increased pancreatic intraductal pressure, resulting from pancreatic ductal obstruction combined with vigorous secretion of pancreatic juice.[11, 51-53] That alcohol and pancreatitis have been closely associated has been stressed for some years.[54-66] The mechanism by which alcoholic overindulgence so frequently precipitates bouts of pancreatitis remains somewhat speculative, but it has seemed reasonable that alcohol may play a dual role, effecting at once obstruction to the outflow of pancreatic juice and stimulation of the pancreas to secrete vigorously. Whatever the mechanism, in the dog at least, Menguy and associates [53] have shown clearly that instillation of ethyl alcohol into the duodenum brings about marked increase in pancreatic intraductal pressure, as well as increased resistance of the pancreatic sphincteric mechanism.

In considerations of this hypersecretion-obstruction theory of the pathogenesis of pancreatitis, the so-called acid-secretin mechanism has often been mentioned as an important factor.[61, 62, 64, 65, 67] It has been suggested that a chief factor in alcohol-induced external pancreatic secretion is the elaboration of hydrochloric acid by the gastric mucosa in response to the stimulus of alcohol; the acid gastric contents on entering the duodenum effect the release of secretin from the mucosa of the upper part of the small intestine, thereby stimulating the pancreas to secrete vigorously.

In view of the emphasis which has been placed on the so-called acid-secretin mechanism, it seems worth noting that pancreatitis can occur despite inability of the gastric mucous membrane to secrete hydrochloric acid. Hallenbeck and I [68] have observed a few such patients, and there have been previous sporadic references in the literature to similar patients, in a few of whom subtotal gastrectomy had been performed.[2, 40, 63, 69, 70] In our cases pancreatitis was sometimes precipitated by alcoholic excesses but at other times occurred without precipitation by alcohol. In light of these clinical observations it is interesting that McClure,[71] McClure and Jones [72] and Christiansen [73] demonstrated normal pancreatic enzymatic activity in patients with achylia gastrica.

The occurrence of pancreatitis despite achlorhydria indicates that hydrochloric acid is not essential for the development of pancreatitis. This observation does not detract from the plausibility of the hypersecretion-obstruction theory of the pathogenesis of pancreatitis. However, in patients with achlorhydria it is clear that the secretion of hydrochloric acid by the gastric mucosa can play no role in the pathogenesis of the disease, and that other factors must be operative. Obstruction of the pancreatic duct may be initiated by spasm or edema in the region of the papilla of Vater, perhaps secondary to the local effects of alcohol or to emotional influences; pancreatitic edema, hemorrhage and necrosis, and postpancreatitic fibrosis and

calcification, may all perpetuate the inflammatory process by adding to pancreatic ductal obstruction. Stimulation of the pancreas to secrete against this obstruction may result from the presence of the breakdown products of the various foodstuffs in the intestine, and in this connection, secretin, pancreozymin and the vagal nerves may all be involved.

Pancreatitis and Hyperlipemia

Intriguing but poorly understood is the association of pancreatitis with hyperlipemia, which is usually (but not always) reflected in grossly visible turbidity (lactescence, opalescence, or milky appearance) of the serum, and which is characterized chemically by increased concentration of the neutral fat primarily, with less marked rises of the cholesterol and phospholipid contents. Cutaneous xanthomas and lipemia retinalis are sometimes evident.

Over the course of a century pancreatitis and hyperlipemia have been reported to coexist in approximately 40 cases,[11, 19, 20, 74-91] although, as far as could be ascertained, there have been only 17 cases where the diagnosis of pancreatitis was confirmed at surgical exploration or at necropsy and where the hyperlipemia was chemically determined.[11, 19, 20, 74-82] In some 25 cases the hyperlipemia was chemically quantitated, but the diagnosis of pancreatitis was based on clinical evidence alone.[20, 81-90] In addition, Edmondson and associates [90-91] have reported two cases where the pancreatitis was definite at necropsy but where no chemical studies of serum lipids had been performed; in one of these cases [90] necropsy revealed a peculiar plum color to the blood which prompted the suspicion that the patient had had hyperlipemia ante mortem, whereas in the other,[91] turbid serum had been observed before death. Edmondson and co-workers [91] also alluded to one case in which pancreatitis was suspected on clinical grounds and in which the serum was milky.

Cases 4 and 5 are examples of recurrent pancreatitis and hyperlipemia.

Case 4. A 32 year old Negro was admitted to the hospital November 2, 1953, because of severe periumbilical pain and nausea for the preceding 16 hours. He had experienced recurrent attacks of such pain for the preceding month. On examination the patient appeared to be in pain. The blood pressure measured 120/80 mm. of Hg. The abdomen was generally tender, particularly in the epigastrium and right upper abdominal quadrant, and rebound tenderness was referred to the epigastrium. There was no fever. Routine urinalysis was negative except for an occasional erythrocyte per high power field in the centrifuged sediment. The leukocytes numbered 13,400 per cubic millimeter of blood, with 82% neutrophilic polymorphonuclear leukocytes. The value for serum amylase was elevated to 533 units (upper limit of normal, 320 units); the serum was turbid.

The patient was observed overnight, and by the next morning the concentrations of serum amylase and lipase were normal. The abdominal findings persisted, however, and the possibility of acute appendicitis could not be excluded. Surgical exploration was therefore carried out, at which time the head of the pancreas was found to be hard and indurated, and there were adjacent scattered areas of fat necrosis. The gall-bladder and common bile duct were normal, as were the stomach and

duodenum. The appendix was removed. Postoperatively the patient had considerable epigastric and right subcostal pain for six days, following which time he became asymptomatic.

The patient returned to the clinic March 28, 1955, and stated that he had continued to experience recurring mild aching in the central and left upper parts of the abdomen since the previous visit. During an episode he usually lay on his right side with knees drawn up to chest, clenching the upper part of the abdomen. He had experienced three fairly severe attacks of abdominal pain during the three weeks prior to his return, one of which had persisted for 48 hours. The attacks were followed by tenderness in the midabdomen and left hypochondrium for two or three days. He was unaware of any precipitating factors. Mild ache in the left upper abdominal quadrant had begun on the day of examination. Physical examination on that date revealed no significant abnormalities. However, two days later the patient reported that the abdominal pain had continued and had increased greatly in severity. He was restless and was obviously having severe epigastric pain. He sat slumped forward, with arms clasped across the upper part of the abdomen. There was marked tenderness across the abdomen just below the navel, and the body temperature measured 100.2° F.

On March 30, the patient was admitted to the hospital and on that day the serum was again noted to be fatty. The fasting blood sugar measured 100 mg. per 100 ml., and the concentrations of serum amylase and lipase were normal. Roentgenograms of the pancreatic area revealed no calcification, and cholecystography disclosed nothing abnormal. The abdominal pain resulting in his admission to the hospital lasted altogether for 84 hours. Values for the plasma lipids were as follows: cholesterol, 234 mg. per 100 ml.; fatty acids, 648; total lipids, 882, slight (but definite) elevations. On April 4, 1955, at surgical reëxploration of the abdomen, chronic pancreatitis was confirmed and transduodenal sphincterotomy was performed. The gall-bladder was normal. The common bile duct was opened and no abnormality discovered.

In the immediate postoperative period the patient continued to experience epigastric and left upper abdominal pain, but this had subsided by the time of his dismissal from the hospital on April 19, 1955, and he remained free of pain during the four months that the T tube was in the common duct.

The patient returned to the clinic in July, 1956, at which time he mentioned recurrent mild pain across the midabdomen once or twice a month, lasting for five minutes to three hours. Abdominal examination was not remarkable, and the values for serum amylase, lipase and bilirubin and for plasma lipids were all normal. The serum was clear at this time. The plasma cholesterol measured 210 mg. per 100 ml.; cholesterol esters, 129; phospholipids, 188; fatty acids, 303; total lipids, 513. In the 18 months following that visit the patient has continued to experience occasional attacks of upper abdominal pain of moderate severity.

The patient knew of no similar occurrences in his family, nor had any of the blood relatives been reported to have hyperlipemia.

Case 5. This 24 year old Negro female came to the clinic in November, 1951, because of recurrent bouts of severe, colicky pain across the entire upper part of the abdomen, referred to the interscapular region, during the preceding year. In May, 1951, after seven months of recurrent attacks, the gall-bladder had been removed elsewhere and was said to have contained "100 stones." The common bile duct presumably had not been explored at that operation. Postoperatively the attacks of pain continued, and four severe attacks had occurred in the two months prior to her examination at the clinic. The pain had become more severe and steady four or five hours after onset, and had lasted as long as three days with some of the attacks; residual epigastric tenderness had been noted. One attack, two months previously,

had been associated with moderately high fever and urine "the color of tea." For three years the patient had experienced rather vague "gas pains" in the epigastrium. She had lost 30 pounds in two years.

Physical examination was not remarkable except for moderate tenderness in both hypochondria and the right lower abdominal quadrant; it was most marked in the left hypochondrium.

Urinalysis revealed only slight albuminuria. The leukocyte count was 7300 per cubic millimeter, and the sedimentation rate was 57 mm. in one hour by the Westergren method. Values for serum amylase and lipase were normal. It was impossible to obtain accurate values for serum bilirubin, inasmuch as the serum was too turbid. The concentration of plasma cholesterol was 236 mg. per 100 ml.; cholesterol esters, 106; phospholipids, 320; fatty acids, 1,860; and total lipids, 2,096. The turbid serum failed to clear in vitro after the addition of 50 mg. of heparin. The sulfobromophthalein (bromsulfalein) test gave a normal result. Roentgenologic study of the esophagus, stomach and duodenum showed no abnormalities.

On December 8, 1951, at surgical exploration, the pancreas was found to be indurated throughout. The common bile duct, liver, stomach and other abdominal organs were normal. Pancreatic biopsy revealed slight periductal fibrosis. Transduodenal sphincterotomy was performed, and a T tube was left in the common bile duct for six weeks. The patient continued to have abdominal pain for the four days immediately following operation, and in October, 1955, she indicated that she had continued to experience recurring bouts of right upper abdominal pain referred through to the back.

The relationship between pancreatitis and hyperlipemia remains puzzling. It is immediately apparent that the mere concurrence of any two such phenomena does not establish a direct cause-and-effect relationship between the two. The number of cases of coexistent hyperlipemia and pancreatitis is still small enough that the two conditions conceivably could represent chance coexistence in these few persons. However, there is some circumstantial evidence to suggest that the relationship between pancreatitis and hyperlipemia is more than casual.

The preponderance of opinion would seem to be that in most instances when pancreatitis and hyperlipemia are associated, the pancreatitis led to the hyperlipemia. Binet and associates [76, 92] produced pancreatitis experimentally in the dog and observed concomitant elevations of the plasma lipid values, as well as turbid serum. More recently Wang and associates [89, 93] performed similar experiments in rabbits and dogs and also observed transient hyperlipemia. Both groups of workers inclined to the view that the pancreatitis had produced the hyperlipemia, although there was no direct evidence to support this inference.

When one is considering the possibility that pancreatitis may lead to hyperlipemia, several other lines of evidence are of interest. The first is the observation, by various workers, [90, 94–96] of fat embolization associated with pancreatitis. The photomicrographs in the paper of Edmondson and Fields [90] show lipid in lymphatics and veins in areas of pancreatic necrosis, and these workers considered that the lipid in the areas of pancreatic necrosis was the source for the widespread fat embolization observed in their case.

Lynch [95] made similar observations; widespread fat embolization, including embolization of the kidneys, was demonstrated at necropsy in three such cases. Another recent development bearing on the possibility that pancreatitis may induce hyperlipemia is the evidence suggesting that the pancreatic islet alpha cells may secrete a hormone which regulates cholesterol metabolism. Caren and Carbo [97] observed hyperlipemia (hypercholesterolemia and turbid serum) regularly in rabbits after administration of cobaltous chloride, which is said to destroy the alpha cells of the pancreatic islets rather selectively. These workers were inclined to discount the possibility that the observed hypercholesterolemia may have been related to some mechanism other than destruction of the alpha cells. Orvis and Evans' [88, 98] studies of hyperlipemia associated with pancreatitis in one patient revealed that most of the lipid was in the beta-lipoprotein fraction as determined electrophoretically. Their studies of clearing factor suggested to them the presence in the serum of an endogenous inhibitor of the patient's lipoprotein lipase. These workers concluded that the hyperlipemia in their patient had resulted from mobilization of endogenous lipid, probably as a result of increased serum lipase.

Another of the possibilities is that hyperlipemia may lead to pancreatitis. Klatskin and associates [79, 82] recently reviewed this matter and postulated that embolization of agglutinated serum lipid particles may induce pancreatitis in some persons. They also suggested fat embolization to viscera other than the pancreas as a possible basis for some of the abdominal crises observed in persons with hyperlipemia. It seems well established that some persons with familial hyperlipemia are predisposed to recurrent attacks of rather severe abdominal pain. Active pancreatitis has existed in some of these persons. The question then arises whether all crises of abdominal pain occurring in those with hyperlipemia represent pancreatitis. Occasionally it has been suggested [99–102] that there were other, somewhat obscure bases for such abdominal pain. Although careful review of the reported cases does not resolve the issue, it would appear that so far there has been no demonstration of any basis other than pancreatitis for such attacks. Therefore, if one grants the possibility that pancreatitis may provoke hyperlipemia in some way, the apparent predisposition toward recurrent pancreatitis in persons with familial hyperlipemia still requires explanation. Perhaps some intermediate metabolic or physiologic derangement gives rise to both the pancreatitis and the hyperlipemia, although this possibility remains only conjectural at present.

Pancreatitis and hyperlipemia may coexist more frequently than is recognized, for studies of serum lipids have been performed infrequently on persons suspected of having pancreatitis unless turbidity of the serum was noted at the time that serum was obtained for other chemical determinations. Future studies should eventually clarify the relationship between pancreatitis and hyperlipemia.

Concluding Remarks

Although these recent developments pertaining to pancreatitis may serve as much to confound as to clarify, it has seemed worth while to summarize the present state of our knowledge about them, perhaps stimulating further studies directed along these and similar paths. Closer and more extended study of such phenomena may eventually result in a better understanding of the etiology and pathogenesis of pancreatitis, and thereby make possible more rational and successful therapy of the disease.

Summario in Interlingua

Es presentate un revista de certe recente disveloppamentos in le studio de pancreatitis. In le curso del anno 1956, 125 casos de pancreatitis esseva vidite al Clinica Mayo. Ex le 75 patientes con chronic pancreatitis recidivante, quasi exactemente un medietate habeva sequellas del morbo. Cinque pro cento del 125 patientes habeva pancreatitis chronic sin dolor, 13% habeva pancreatitis hereditari.

Le diagnose de pancreatitis chronic sin dolor depende del demonstration de sequellas del morbo o del obtention de provas chirurgic o histologic. Il pare que acute o subacute pancreatitis interstitial pote occurrer similemente sin annuncio in le forma de dolores abdominal de grados considerabile de severitate.

Pancreatitis hereditari, observate depost 1952 in plure gruppos de consanguineos, se declara characteristicamente durante le pueritia e es transmittite in le familias afficite per illo in le forma de un tracto mendelian dominante non ligate al sexo. Studios de essayage microbiologic de amino-acidos ha revelate excessos del excretion urinari de lysina in subjectos con pancreatitis hereditari e, in alicun casos, in apparentemente normal .consanguineos de tal subjectos. Le mechanismo e le signification del amino-aciduria ha non ancora essite determinate.

Le co-existentia de hyperparathyroidismo con pancreatitis o calcification pancreatic es describite in 15 casos. Si o non hyperparathyroidismo predispone al disveloppamento de pancreatitis remane un question aperte.

Le occurrentia de pancreatitis in personas con achlorhydria es notate e indica que le secretion de acido hydrochloric per le mucosa gastric non es un sine qua non in le pathogenese de pancreatitis.

Hyperlipemia e pancreatitis se trovava combinate in un micre numero de casos. Iste co-existentia subleva le question de un possibile relation etiologic. Nulle tal ha usque nunc essite demonstrate.

Le studio meticulose del mentionate e de altere simile anormalitates que se trova a vices associate con pancreatitis promitte resultar in le curso del tempore in un clarificate comprension de factores etiologic e pathogenetic de pancreatitis e consequentemente in plus rational e plus efficace therapias de ille condition.

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FAT ABSORPTION AND PANCREATIC FUNCTION IN DIABETES MELLITUS *

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ABNORMALITIES in the exocrine secretion of the pancreas following intravenous secretin stimulation [1, 4, 13, 14] and defective fat absorption as a rare complication of diabetes mellitus [3, 10] have been previously reported. Acinar sclerosis and visceral neuropathy were thought to be responsible for these respective findings. Such recorded observations led us to a combined study of fat absorption and exocrine function of the pancreas in a controlled group of diabetic patients. Two of these were complicated by nocturnal diarrhea.

MATERIALS AND METHODS

Studies were carried out on 10 selected control patients and 10 diabetic patients. Two of the control cases had organic lesions (duodenal ulcer and arteriosclerotic heart disease), and the remaining eight patients had functional gastrointestinal problems. None in this control group had either diabetes mellitus or pancreatic disease.

Six of the 10 diabetics were simple, uncomplicated cases; the remaining four were complicated by diarrhea. In one of these four (case 23), the diabetes was secondary to a chronic relapsing pancreatitis, thus differing from the other nine cases.

For the study of fat absorption a chemical fat balance technic and an I^{131} iodotriolein absorption test were used. Patients were kept on a diet containing a fixed amount of fat (usually 100 gm. daily) for the fat balance study. Feces were collected for three or more consecutive days, starting 48 hours after the institution of the special diet. The fecal fat content was determined in an aliquot wet sample. All feces excreted over a three- or four-day collection period were transferred to a Waring Blendor and, after sufficient distilled water had been added the material was mixed thoroughly for several minutes. An aliquot sample of this mixture containing about 5 gm. of feces was tested for fat content by the method of Van de Kamer et al.[21] This assumes a molecular weight of 297 for fat. The total fat ingested and excreted during the collection period was calculated. Results of the fat balance study were expressed as "per cent excretion," $\frac{\text{fat excreted}}{\text{fat ingested}}$

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$\times$ 100, or as "coefficient of absorption," C.A., $\frac{\text{fat ingested} - \text{fat excreted}}{\text{fat ingested}}$ $\times$ 100. Five per cent excretion was considered to be the upper limit of normal.

The I^{131} iodotriolein absorption test was performed as follows: 25 μc of tagged triolein * were given by mouth in 5 c.c. of olive oil, 5 c.c. of distilled water, and 0.5 c.c. of Tween 80. The stools were collected in individual containers. To obtain at least two stools after tracer studies were started, the collection period was usually continued for from 48 to 96 hours. Samples were counted in the original, individual containers, using a Nancy Wood

TABLE 1
Control Patients

Case No.	Age	Secretin Test		Fat Balance Studies			Radioactive Triolein Test Per Cent Excretion
		Volume c.c./Kg. of Body Weight	Maximal Bicarbonate Concentration, mEq./L.	Stool Collection in Days	C.A.	Per Cent Excretion	
1	39	5.0	103.9	8	95.8	4.2	1.0
2	24	3.6	105.6	9	95.6	4.4	3.1
3	49	2.6	105.5	8	96.7	3.3	2.3
4	36	5.4	84.3	5	96.2	3.8	1.5
5	44	4.3	116.5	5	97.5	2.5	3.4
6	43	6.1	127.1	2	98.8	1.1	2.6
7	35	4.0	97.2	3	98.4	1.5	4.6
8	67	5.0	119.3	3	96.5	3.4	3.2
9	48	3.4	112.1	3	98.4	1.5	1.9
10	63	2.9	115.3				
	Mean ± s.d.	4.2 1.4			Mean ± s.d.	2.9 1.2	2.6 1.1

scintillation counter. The radioactivity in the stool was compared with the standard, and the percentage of fecal excretion was calculated. Five per cent was used as the upper limit of normal excretion as established by the control group.

In most of the cases studied, chemical fat determinations were performed on the same stool samples containing the isotope tracer for parallel determinations. This was not done in every case, however, since tracer studies usually require only a 48-hour collection, whereas collecting periods of three or more days are usually desirable for chemical analysis.

In the study of the exocrine function of the pancreas, the intravenous secretin test of Lagerlöf and Diamond as standardized by Dreiling was used.[6] A double lumen duodenal tube was passed in the fasting patient and positioned under fluoroscopic control so that the tip of the tube was in the third portion of the duodenum. With gentle suction, gastric and duodenal contents were drained separately. Intravenous secretin,† 1 clinical

* Obtained from Abbott Laboratories, Oak Ridge, Tennessee.
† Secretin, Lilly. Generously supplied by Eli Lilly and Company.

unit per kilogram of body weight, was given and the duodenal contents were collected fractionally for 80 minutes. Ninety milliequivalents per liter or higher were used as the normal bicarbonate value. Two cubic centimeters or more per kilogram of body weight of pancreatic juice were used as the normal volume.

Results

Table 1 summarizes the results obtained in the controls. The secretin test shows normal values of volume and maximal bicarbonate concentration except in case 4. Although the bicarbonate concentration is slightly below 90 mEq./L. in this case, experience with the secretin test reveals that this

Table 2

Diabetic Patients

Case No.	Age	Duration of Diabetes, Years	Secretin Test		Fat Balance Studies			Radioactive Triolein Test, Per Cent Excretion	Comments
			Volume c.c./Kg. of Body Weight	Maximal Bicarbonate Concentration mEq./L.	Stool Collection in Days	C.A.	Per Cent Excretion		
11	24	<1	2.2	96.1	4	98.0	2.0	1.0	
12	43	4	3.5	105.9	5	98.9	1.0	0.8	
13	58	7	2.0	110.2	Not performed				
14	33	10	Unsuccessful		3	98.2	1.7	0.8	
15	64	3	2.5	99.7	3	98.1	1.9	1.3	
16	42	10	3.9	114.0	Not performed				
21	29	10	2.2	140.0	9	83.7	16.3*	19.4*	Nocturnal diarrhea
22	68	1	2.0	89.6	6	84.6	15.4*	25.7*	Chronic diarrhea
23	50	2	4.6	65.8	12	91.8	8.2*	7.5*	Chronic pancreatitis
24	51	10	5.0	128.8	3	98.7	1.3	2.9	Nocturnal diarrhea, ASHD
		Mean ± s.d.	3.1 1.1			Mean ± s.d.	1.6 0.4	1.9 1.0	

* Not used in calculation of standard deviation.

may still be considered to be a low normal. The fat balance studies reveal that all patients absorbed more than 95% of the ingested fat, or that less than 5% was excreted. (The mean for nine cases is 2.9 ± 1.2% excreted.) The tagged triolein excretion was below 5% in this group and in an additional six other normals not shown in table 1. The mean value for these nine control cases was 2.6 ± 1.1% excretion. Comparison of the results obtained by both methods is not entirely justifiable, as has been explained above; nevertheless, the difference in values obtained by the two methods is clinically insignificant in most cases.

The results obtained in the 10 diabetic patients are shown in table 2. One secretin test was unsuccessful (case 14), and only one was abnormal (case 23). This last patient was a 50 year old man with known diabetes for two years. His original diagnosis was that of diabetes mellitus. He

was admitted for treatment of a peripheral arterial insufficiency and for diabetic management. A careful review of his history revealed that he had formerly been a heavy drinker and had had frequent attacks of severe epigastric and right upper quadrant pain. Although x-rays failed to show any pancreatic calcification, the clinical impression was that of chronic pancreatitis with involvement of the islet cells, rather than diabetes mellitus. The abnormal secretin test confirmed this impression.

Table 2 shows that fat absorption is not abnormal in uncomplicated diabetes (cases 11, 12, 14 and 15). In case 23 a mild steatorrhea secondary to pancreatic insufficiency was demonstrated. The remaining three cases (cases 21, 22 and 24) will be presented more fully.

Case Reports

Case 21. A 29 year old white man with poorly controlled diabetes of 10 years' duration developed attacks of moderately severe nocturnal diarrhea in November, 1956. These consisted of from six to 10 watery bowel movements nightly between midnight and 8:00 a.m. He also had occasional fecal incontinence at night. After a diarrheal attack, normal bowel function returned for a few days or weeks. Physical examination, including neurologic examination, was negative. There were no genitourinary symptoms, and a cystometrogram was normal. Other symptoms and signs suggesting autonomic neuropathy, such as postural hypotension, impotence and pupillary abnormalities, were also lacking. Laboratory studies revealed a moderately severe diabetes. X-rays, including small bowel studies, were normal except for marked pylorospasm as seen fluoroscopically, with total retention of barium lasting at least one and one-half hours. Because of this the secretin test was rather difficult to perform and was successful only on a third trial. Fat absorption studies in this case revealed moderate steatorrhea, the triolein excretion being 19.4% and the fat excretion by the balance technic being 16.2% over a nine-day period. No relation of high blood sugar to the diarrhea was observed. Banthine and pancreatin had no effect on the diarrhea.

Comment: This patient represents a case of poorly controlled, moderately severe diabetes in a young man, complicated by nocturnal diarrhea and mild steatorrhea during his diarrheal attacks.

Case 22. This was a 68 year old white man with a history of chronic functional diarrhea over many years which had become markedly increased in intensity during the last year and necessitated hospitalization. A mild diabetes was discovered at this admission. Physical examination revealed diabetic neuropathy, manifested by paresthesias, unequal reflexes, and impaired vibratory sensation in the lower extremities. Diarrhea was not nocturnal in this case but consisted of rather severe attacks, with 10 to 20 watery bowel movements daily containing undigested food and associated with some incontinence. Fat absorption studies in this case during a diarrheal episode revealed a mild to moderate steatorrhea. The difference in results obtained by the chemical and the radioactive methods seems remarkable in this case. Technical difficulties in carrying out the balance studies because of the numerous bowel movements may be responsible for this discrepancy.

Comment: This is a case of long-standing functional diarrhea, recently increased in severity, with the concomitant appearance of diabetes compli-

cated by neuropathy. Moderate steatorrhea appeared during the diarrheal episodes. This case probably represents a combination of functional and diabetic diarrhea.

Case 24. This 51 year old Negro man had been diagnosed as having diabetes in July, 1947. He accepted management for a year only and then stopped his diabetic diet and insulin. He was admitted to the hospital for the second time in February, 1957, for hypertensive cardiovascular disease with congestive failure. Approximately four months before admission he developed nocturnal diarrhea with some incontinence. He usually awakened around 2:00 or 3:00 a.m. with diarrhea and had from three to five watery stools until early morning. On physical examination no signs of peripheral neuropathy could be demonstrated. Laboratory and x-ray studies revealed a moderate diabetes and marked delayed gastric emptying, with pylorospasm as seen fluoroscopically, similar to that encountered in case 21; however, the secretin test was not so difficult technically. The diarrhea stopped following control of his diabetes. Fat absorption studies performed during this remission were completely within normal limits.

Comment: This is a case of uncontrolled diabetes of at least 10 years' duration in a 51 year old man, complicated by nocturnal diarrhea. No fat absorption defect could be demonstrated during a remission of his diarrhea.

Discussion

Secretin test studies on patients with diabetes mellitus are not numerous. A review of the literature is summarized in table 3. Up to 1951 only twenty-one cases had been reported. Abnormal results were found in 13. In 1943 Pollard et al.[14] expressed the opinion that definite abnormalities could be expected in secretin tests in patients with diabetes if the disease was of three years' duration or longer because of associated acinar sclerosis. This was in accordance with a report on pancreatic function in diabetics by Jones et al.[9] in a larger series studied by a different method. These authors used a single lumen tube and a cream solution for stimulation. Grossman and Ivy demonstrated experimentally that in alloxan diabetes in the dog there is a suppression of the exocrine secretion of the pancreas, as indicated by an increase in the amount of secretin required to initiate secretion.[8] However, enzyme secretion remained normal.

In 1951 Dreiling[5] obtained altogether different results in diabetics studied by the secretin test. Among 62 cases only 27 were abnormal, and 25 of the latter had proved pancreatic disease, either inflammatory or neoplastic. According to Dreiling, the test is normal in uncomplicated diabetes mellitus. Such laboratory information may be of value in the differential diagnosis of diabetes mellitus, as distinguished from neoplastic or inflammatory pancreatic disease producing diabetes. The present study, although it is not large enough to draw decisive conclusions, confirms Dreiling's findings.

No information could be found in the literature about fat absorption in uncomplicated diabetes. Four uncomplicated diabetics in the present series,

studied by two different methods, show that fat absorption is within normal limits.

There are a few reports concerned with diabetes complicated by diarrhea. Table 4 is a compilation of these reports on diabetic diarrhea found in the literature since Bargen et al.[2] first described the condition in 1936. As the review of the literature demonstrates, "diarrhea of diabetes" is a rather infrequent complication. In three large series of patients with diabetic neuropathy the incidence of diarrhea was found to be 5, 18 and 21.6%, respectively.

TABLE 3

Reports in the Literature on Secretin Tests in Patients with Diabetes

Authors	Year	No. of Cases Studied	No. with Abnormal Results	Comment
Ågren, Lagerlöf, Bergland[1]	1936	4	2	One abnormal result was in a patient with pancreatitis.
Diamond, Siegel[4]	1940	4	3	One abnormal result was in a patient with acute edema of the pancreas.
Pollard, Miller, Brewer[13]	1942	6 } 13	8	One abnormal result was in a patient with associated steatorrhea.
Pollard, Miller, Brewer[14]	1943	7 }		
Dreiling[5]	1951	62	27	25 of the abnormal results were in patients with pancreatic disease (inflammatory or neoplastic).
Present study	1957	9	1	This one abnormal result was in a case of chronic pancreatitis.

Among the 122 cases summarized in table 4, only 48 have information about fat absorption. Rundles[18] reports that "stool examinations in the hospital failed to reveal excess fat" in 27 diabetics with diarrhea. Whether balance studies were performed in these is not mentioned. Landabure[10] the first to call attention to the association of diabetes and steatorrhea, reported eight cases with detailed balance studies. However, most of the cases in this series are examples of pancreatic lesions manifested by diabetes and pancreatic steatorrhea. Of 27 cases of diabetic diarrhea reported by Martin,[11] only two were studied for steatorrhea by a fat balance technic, and normal results were obtained. Recently Berge and his collaborators[8] reported six cases of steatorrhea complicating diabetes mellitus with neuropathy. The possible association of pancreatic lesions or other disorders which result in steatorrhea was considered and excluded. The authors tended to accept the etiologic role of autonomic neuropathy involving the intestinal tract as an explanation for the steatorrhea. To this series of six they added short histories of two additional diabetics with associated diarrhea and steatorrhea in the absence of definite evidence of diabetic neuropathy. One of the two cases of nocturnal diarrhea reported in the present study

(case 21) is similar to these. Careful search for impaired fat absorption in the second (case 24) failed to reveal steatorrhea during a remission.

Unfortunately, repeat absorption tests were not performed in these two cases to investigate the possible role of rapid intestinal passage in the pathogenesis of the steatorrhea. Significant differences of fat absorption in these two otherwise clinically similar cases, however, suggest that increased intestinal motility, rather than a defect in digestion or absorption, may be responsible for the mild steatorrhea encountered in some cases of diabetic diarrhea. Studies in the future with the newly developed intestinal biopsy technic and radioactive oleic acid may help to clarify the problem further and to differentiate it from other types of steatorrhea.

TABLE 4

Reports in the Literature on the Diarrhea of Diabetes

Authors	Year	No. of Cases Studied	No. with Steatorrhea	Comment
Rudy[15]	1940	1		No fat absorption study.
Rundles[17]	1945	27	None	Among 125 cases of diabetic neuropathy, 27 had diarrhea.
Rudy, Epstein[16]	1945	5		Among 100 cases of diabetic neuropathy, five had diarrhea. No fat studies performed.
Sheridan, Baily[19]	1946	40		No fat absorption studies.
Landabure et al.[10]	1948	8	8	Most of these cases are compatible with pancreatic insufficiency, when carefully analyzed.
Muri[12]	1953	1		No fat absorption study.
Goodman et al.[7]	1953	2		No fat absorption studies.
Martin[11]	1953	27		Among 150 cases of diabetic neuropathy, 27 had diarrhea. No steatorrhea was found in the two cases studied.
Berge et al.[3]	1956	6 2	6 2	All six had diabetic neuropathy and steatorrhea. The two additional cases reported had steatorrhea without neuropathy.
Present study	1952	3	2	Only one patient with steatorrhea demonstrated peripheral neuropathy. In the patient who did not show steatorrhea, fat absorption studies were performed during remission of diarrhea.

SUMMARY

1. Results of fat absorption studies and pancreatic function studies in 10 diabetic patients and 10 control patients are reported.

2. Fat absorption was determined by radioactive I^{131} triolein and chemical fat balance methods. Pancreatic function was evaluated by the intravenous secretin test.

3. The secretin test was normal in both groups except for one patient with diabetes secondary to chronic pancreatitis.

4. All fat absorption studies were normal in the uncomplicated diabetic patients.

5. Mild steatorrhea was found in two patients with diabetic diarrhea during a diarrheal attack. One of these patients had nocturnal diarrhea. In a third patient with a diagnosis of nocturnal diarrhea, normal values were obtained during a remission.

6. A review of the literature on diabetes complicated by diarrhea is presented and briefly discussed.

Summario in Interlingua

Es presentate un studio del absorption de grassia e del function exocrin del pancreas in 10 seligite patientes de controlo e in 10 patientes diabetic. In sex del 10 diabeticos il se tractava de simple e non-complicate casos. Le casos del remanente quatro esseva complicate per diarrhea. In un del quatro (caso 23), le diabete esseva secondari a relapso de pancreatitis chronic. Duo del 10 subjectos de controlo habeva lesiones organic. Le remanente octo habeva functional problemas gastrointestinal.

Le absorption de grassia esseva studiate per chimo-determinationes del balancia de grassia e per mesurar le excretion de trioleina radioactive. Cinque pro cento esseva acceptate como limite superior de un excretion ancora normal. Iste valor esseva establite per le studio de un gruppo de controlo. Illo esseva usate pro ambe le methodos. Le function exocrin del pancreas esseva studiate per medio del test a secretina intravenose. Novanta milliequivalentes per litro esseva acceptate como limite inferior de un valor ancora normal de bicarbonato. Duo centimetros cubic per kilogramma de peso corporee esseva acceptate como limite inferior de un volumine ancora normal de succo pancreatic.

Esseva trovate que le absorption de grassia in le subjectos de controlo esseva intra le limites normal (tabula 1). Le differentias del valores obtenite secundo le duo methodos esseva clinicamente sin signification. Le test a secretina revelava valores normal, excepte in le caso de un patiente (caso 4) in qui le concentration maximal de bicarbonate esseva levemente infra 90 milliequivalentes per litro.

Le resultatos obtenite in le 10 patientes diabetic es presentate in tabula 2. Le responsa a secretina esseva anormal in le patiente con pancreatitis chronic (caso 23). Le test non succedeva in le caso de un altere diabetico (caso 14). Le absorption de grassia esseva normal in diabete non-complicate (casos 11, 12, 14, e 15). In le caso del patiente con pancreatitis chronic leve grados de steatorrhea esseva demonstrate. Es reportate brevemente le casos del remanente tres diabeticos. Caso 21 esseva illo de un juvene homine con mal controlate e moderatemente sever diabete de 10 annos de duration. Hic le diabete esseva complicate per diarrhea nocturne. Studios del absorption de grassia revelava leve grados de steatorrhea durante le attaccos de diarrhea. Caso 22 representava probabilemente un combination de diarrhea functional e diabetic. Grados moderate de steatorrhea esseva demonstrate durante le episidios de diarrhea. Le ultime patiente (caso 24) habeva un non-controlate diabete de al minus 10 annos de duration, complicate per diarrhea nocturne. Nulle defecto del absorption de grassia poteva esser constatate durante un remission del diarrhea.

Es presentate un breve revista e discussion del litteratura relative a diarrhea de

diabete e relative al resultatos del test a secretina in patientes con diabete mellite (tabulas 3 e 4). Es signalate le possibilitate que augmentos del motilitate intestinal plus tosto que defectos del digestion e del absorption es responsabile pro le leve grados de steatorrhea que es incontrate in certe casos de diarrhea diabetic.

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HEREDITARY HYPERPARATHYROIDISM ASSOCIATED WITH RECURRENT PANCREATITIS *†

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THE purpose of this paper is to report six and possibly seven cases of hyperparathyroidism in two generations of one family, associated with recurrent pancreatitis in at least two instances. The hyperparathyroidism was proved in two brothers, a maternal uncle and aunt by excision of parathyroid adenomas, and was established in their mother and another uncle by repeated chemical abnormalities. Reports of hereditary pancreatitis by Gross and Comfort [1, 2] and Comfort and Steinberg [3] stimulated an investigation of the family of two brothers who had had repeated attacks of pancreatitis. A serum calcium obtained on the mother after an episode of abdominal pain was unexpectedly found to be elevated to 12 mg.%. Subsequent investigation of the brothers yielded typical chemical findings of hyperparathyroidism, and a single parathyroid adenoma was removed from each. Further studies revealed evidence of hyperparathyroidism in four of six of the mother's siblings. The pedigree of this family is shown in figure 1.

CASE REPORTS

II–2. This 50 year old female was seen originally because of abdominal pain radiating into the back, associated with nausea and vomiting similar to episodes she had had in the past. Because two of her three sons had recurrent pancreatitis, efforts were made to determine if she might also have this condition and, unexpectedly, an elevated calcium was found. Her serum amylase was not elevated, but her serum lipase was 1.7 c.c. 0.05 N sodium hydroxide. The serum calcium elevation was later confirmed, and the phosphorus was found to be 3 mg.%. Pancreatic calcification and nephrocalcinosis were not demonstrated. She had mild diabetes mellitus, requiring about 15 units of insulin. Her father had died in his sixties of an ulcer, and her mother had died in the early seventies with diabetes mellitus. Parathyroid exploration is planned in the future.

III–2. This 29 year old son of II–2 was seen in July, 1950, with abdominal pain, nausea and vomiting, at which time the serum amylase was 250 units. An exploratory laparotomy was performed, and marked edema of the omentum and pancreas was noted, without evidence of hemorrhagic necrosis. Incidentally, at this time the serum calcium was 13 to 14 mg.% on three separate occasions but this was considered to be a laboratory error. Subsequent episodes of abdominal pain were associated with amylase elevations to 300 and a lipase elevation to 2.5 c.c. of 0.05 normal sodium hydroxide. In June, 1954, the patient was seen because of weight loss with anorexia, frequent watery stools and vomiting. He had noted increased thirst and nocturia. The stools were negative for trypsin on two occasions; his

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glucose tolerance test was normal; the calcium was reported as 9.7 mg.%, and phosphorus, 3.8 mg.%. In December, 1956, further studies, undertaken because of the findings in his mother, revealed: serum calcium, 13 mg.%; serum phosphorus, 3 mg.% (repeatedly); alkaline phosphatase, 3.0 Bodansky units; normal blood urea nitrogen; a value for the tubular reabsorption of phosphorus (T.R.P.) 65%; glucose tolerance curve, mildly diabetic. X-rays revealed diffuse calcification in the pancreas,

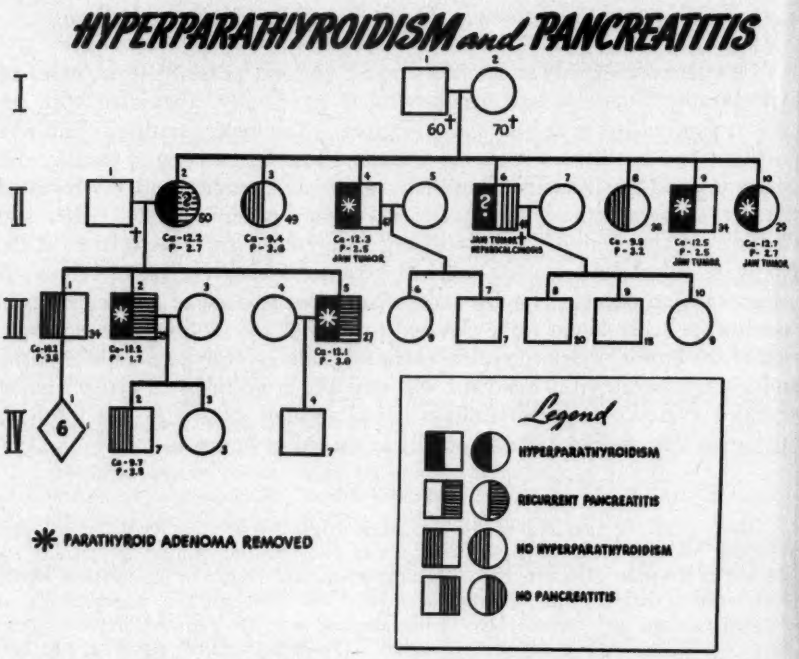

FIG. 1. Pedigree of family showing the association of hyperparathyroidism with recurrent pancreatitis. Calcium and phosphorus values are in milligrams per cent. The squares indicate males, the circles indicate females, and the diamond enclosing the figure 6 indicates six children of both sexes. The ages are given in the lower right area of each figure. The crosses indicate that the individual is dead. The blank spaces indicate that definite information was not available regarding hyperparathyroidism or pancreatitis in those individuals.

with no calcification noted in the kidneys. The skull x-rays showed diffuse rarefaction of the calvarium; the dental x-rays were normal. A solitary 5 gm. adenoma of the right lower parathyroid gland was removed in December, 1956. After surgery the patient gained weight, was no longer constantly nauseated, was less irritable, and noted a marked decrease in fatigue. Three months after the operation his serum calcium was 8.4 mg.%; phosphorus, 4.6 mg.%; T.R.P., 89%. In the year following surgery he has had no further episodes of abdominal pain despite intake of food and beverages which formerly precipitated attacks.

III–5. This 27 year old son of II–2 and brother of III–2 was first seen in 1948 with vomiting and a weight loss of 40 pounds following a fracture of the lower leg. An appendectomy was performed in 1951 for right lower quadrant pain associated with an elevated white blood count. Recurring episodes of abdominal pain, nausea

and vomiting were established as pancreatitis by serum amylase elevations (as high as 830 units). The serum calcium was found to be elevated to 13 mg.% in December, 1956, after his mother was found to have the elevated serum calcium. No calcification in the pancreas or kidneys was demonstrated, although his dental x-rays showed absence of lamina dura. Prior to surgery in January, 1957, his serum calcium was 13.2 mg.% and serum phosphorus was 1.6 mg.%, with a T.R.P. of 73%. A 4 gm. adenoma of the right lower parathyroid gland was removed. The serum calcium fell to 9 mg.%, with a rise of the T.R.P. to 95%, and in the 11 months following the operation he had no further episodes of abdominal pain despite the intake of food and beverages which formerly would precipitate these attacks. His nausea disappeared, and a marked decrease in nervous irritability was noted.

II–4. This 47 year old brother of II–2 had had tumors of the right maxilla and the left mandible removed in 1949 which were reported to represent fibrous dysplasia or fibrous osteomas. When he was seen in March, 1957, dental x-rays showed cystic areas filled with irregular calcified material in both mandibles. An intravenous pyelogram was normal. The serum calcium values on separate occasions were 11.8, 12.4 and 12.3 mg.%; serum phosphorus levels were 2.0, 2.1 and 2.5 mg.%, and the alkaline phosphatase was 5.9 units. In the fall of 1957 a kidney stone attack prompted further studies, which showed that he excreted 475 mg. of calcium a day on a 135 mg. calcium intake. On December 11, 1957, an adenoma of the right upper parathyroid gland was excised.

II–6. This case report concerns another brother of II–2, who died in 1955 at the age of 40. He was seen initially in 1943 with a tumor of the right maxilla, and in 1952 returned for excision of this tumor, which was found to be composed of osteoid tissue and spicules of bone, and was termed a fibro-osteoma. He had much pain in the right cheek before and after this operation, and was thought to have a trigeminal neuralgia. In 1953, after alcohol injections of the infra-orbital nerve had proved unsuccessful in relieving the pain, a section of the ophthalmic and maxillary roots of the fifth cranial nerve was performed, without relief of pain. Following this surgery the patient had convulsive seizures, and died during one of them. Laboratory studies showed a 2 plus albuminuria during the last year of his life. No calcium studies were performed. Autopsy revealed focal cortical gliosis in the area of previous brain surgery, coronary arteriosclerosis without myocardial infarction, only fatty infiltration in the pancreas, but extensive calcification in the renal papillae. Even though the parathyroid glands were not examined, the location of the calcification in the renal papillae, according to Reifenstein,[4] is almost pathognomonic of hyperparathyroidism. Although we cannot prove the existence of hyperparathyroidism in this individual, it seems likely that he was affected in view of the bone tumor and the nephrocalcinosis.

II–9. This 34 year old brother of II–2 had had a tumor of the mandible removed in 1948 which was diagnosed as fibrous dysplasia of bone. He was found to have a serum calcium of 12.5 and a serum phosphorus of 2.5 mg.% after others in the family had been found to have hyperparathyroidism. These abnormalities were confirmed many times, together with the finding of a T.R.P. of 55%. The kidney x-rays showed diffuse nephrocalcinosis bilaterally. Dental x-rays showed an absence of the lamina dura in some areas. An exploratory neck dissection, performed in February, 1957, revealed no parathyroid adenoma, although a small portion of parathyroid tissue was removed. The calcium levels remained high, and in April, 1957, a mediastinal exploration was performed and again no parathyroid adenoma was found. The blood chemistry values remained abnormal, and further exploratory surgery is contemplated. No evidence of pancreatitis was found in this individual although he reported severe episodes of abdominal pain associated with nausea and vomiting several years prior to the recent studies.

II–10. This 29 year old sister of II–2 had had a tumor of the jaw removed in 1951 which was diagnosed as fibrous dysplasia of bone. The serum calcium was elevated to 12.7 mg.%, and the serum phosphorus was 2.7 mg.%. Her only symptom had been general fatigue until she developed a ureteral calculus in October, 1957. At this time she was found to have bilateral renal calcification, and a serum calcium of 12.4 mg.% with a serum phosphorus of 1.6 mg.%. On December 10, 1957, two parathyroid tumors were removed; the larger, a 1 cm. tumor, lay under the right lower pole of the thyroid gland, the second on the left side.

These serum calcium determinations were performed by the method of Fales [5] as modified in our laboratory by Buckner and Shively.[6] The tubular reabsorption of phosphorus (T.R.P.) was determined as described by Chambers, Gordan, Goldman and Reifenstein.[7]

Discussion

The pedigree of hyperparathyroidism in this family suggests an autosomal dominant type of inheritance, with both males and females affected in two generations. The pedigrees of hyperparathyroidism in the other families reported in the literature are also compatible with a dominant inheritance. Goldman and Smyth [8] in 1936 reported parathyroid adenomas in a 17 year old girl and in her 23 year old brother. Schneider, Kyger and McCullagh [9] reported a 20 year old girl with a dark oxyphil parathyroid tumor whose second cousin once removed had had the same type of tumor. Shallow and Fry [10] reported a 35 year old man who had had parathyroid adenomas removed on two occasions; later his 14 year old daughter had a parathyroid adenoma removed. Frohner and Wolgamot [11] reported hyperparathyroidism in five siblings whose father had had kyphosis, polyuria and weakness, and had died at the age of 63. Nielson [12] reviewed the cases reported by Frohner and Wolgamot and reported hyperparathyroidism in two sisters. Caylor and Talbert,[13] from our institution, following the experience of the family reported here, found a calcium of 12.2 mg.% and a phosphorus of 2.8 mg.% in a 31 year old man with a ureteral calculus. His father, age 55, had a long history of recurring peptic ulcer, and was found to have a calcium of 12.0 mg.% and a phosphorus of 1.7 mg.%. Since the abnormal chemical findings on the father persisted after removal of an 0.17 gm. parathyroid adenoma, it is postulated that he has another adenoma. Since the tendency to adenoma formation in the parathyroid glands may be inherited as a dominant condition, it is suggested that all blood relatives of patients with primary hyperparathyroidism also be evaluated for this condition.

In the family reported here and in the families referred to above, no evidence of adenomas of the pituitary gland or pancreatic islet cells was found, although the adenomas of the parathyroid were multiple in at least two families.[10, 11] It may be that the hereditary tendency to the formation of parathyroid adenomas as seen in these families is the same disease as that described by Wermer [14] as a dominantly inherited adenomatosis of the endocrine glands, and by Moldawer, Nardi and Raker [15] as a concomitance of multiple adenomas of the parathyroids, pancreatic islet cells and the

pituitary. Underdahl, Woolner and Black [16] reported eight cases of multiple endocrine adenomas. One of their patients with hyperparathyroidism and multiple adenomas of the pancreas had a sister who had died in coma after spells of confusion. In another case, a patient with two parathyroid adenomas and hypoglycemic episodes had a brother with cancer of the pancreas. Wermer [14] suggested that a single genetic abnormality could be responsible for the adenoma formation in these endocrine glands. Certainly, cases of adenomas of any of these glands should be investigated for hyperfunction of the others.

In the family reported in this paper, bone tumors occurred in four individuals of the second generation, in each of whom there was evidence of hyperparathyroidism. The familial incidence of osteomas had been noted by Plenk and Gardner,[17] who found normal calcium and phosphorus values in three of six of their patients in whom the osteomas were associated with polyposis of the colon. They found four families in the literature with osteomas without polyposis. One of these, reported as osteitis fibrosa cystica by Sedgenidse,[18] concerned a 16 year old girl, her father and paternal grandfather with multiple tumors of the cranial bones. The occurrence of bone tumors in more than one member of a family suggests the need for investigating the family for evidence of hyperparathyroidism.

The association of pancreatitis with hyperparathyroidism has not been generally appreciated, and in an article on gastrointestinal symptoms in hyperparathyroidism by St. Goar [19] pancreatitis was not mentioned. Bogdonoff, Woods, White and Engel [20] reported pancreatitis occurring as a complication on the second day following removal of a parathyroid adenoma. Pancreatitis as a postoperative complication of parathyroid surgery was also noted by Bell and Arnold [21] and by Hellstrom.[22] One of Hellstrom's [22] other cases of hyperparathyroidism was noted to have calcification of the pancreas as well as of the kidney. A C.P.C. case from the 1956 American College of Physicians' meeting [23] showed pancreatitis terminally in a case of hyperparathyroidism. The pancreas showed interstitial fibrosis and chronic inflammation, but no mention was made as to whether calculi were present in the ducts. Rogers, Keating, Morlock and Barker [24] reported the autopsy of a 68 year old man with marked hyperplasia of the parathyroid glands and calcium deposits throughout the pancreas, along with dilatation of the pancreatic ducts. They considered that the hypercalcemia may have played a part in the development of the pancreatic lithiasis. Martin and Canseco [25] reported 14 cases of pancreatic calcinosis, in one of whom a parathyroid adenoma was found at autopsy. Smith and Cooke [26] reported the autopsy of a patient with a serum calcium of 23 mg.%, a 7 gm. parathyroid adenoma, and a swollen, partially necrotic pancreas in which there was finely divided, widespread pancreatic calcinosis. Cope, Culver, Mixter and Nardi,[27] in reporting two cases of the association of pancreatitis and hyperparathyroidism, suggested that pancreatitis may be a clue to the diagnosis of hyper-

parathyroidism. Plough and Kyle [28] reported the case of a 37 year old man with a history of acute pancreatitis, pancreatic insufficiency and a parathyroid adenoma. They suggested that the hyperparathyroidism may have been caused indirectly by the pancreatic insufficiency. The association of the two diseases in so many instances would seem to be more than coincidence.

One can only speculate at present about the relationship between hyperparathyroidism and recurrent pancreatitis. The most attractive theory would seem to be that the pancreatitis is secondary to stone formation in the pancreatic duct system as a result of the hypercalcemia and alkaline pancreatic secretion. The relief of symptoms of recurrent pancreatitis by parathyroidectomy in the two brothers in this study and in the one case reported by Cope, Culver, Mixter and Nardi [27] also suggests that the pancreatitis was in some ways sequentially related to the hyperparathyroidism. The family reported here, with the pancreatitis present in only a few members affected with hyperparathyroidism, furnishes evidence that the hyperparathyroidism was responsible for the pancreatitis, rather than the parathyroid adenomas being secondary to pancreatic insufficiency.

Hereditary pancreatitis reported by Comfort and Steinberg [3] in one family and by Gross and Comfort [1, 2] in two or three other families seems to be inherited as a dominant condition and to be manifested frequently by pancreatic lithiasis. Calcium values in some of the affected individuals of their families have been found to be normal.[29] The possibility cannot be excluded that hereditary pancreatitis could be coexisting in this family, with the hyperparathyroidism causing the underlying pancreatitis to be manifest more completely. It is planned to perform urinary amino acid studies on affected and nonaffected individuals of this family, following the suggestion of Gross, Comfort and Ulrich [30] that this type of study will help to distinguish the hereditary from the nonhereditary form of pancreatitis.

Summary

The occurrence of parathyroid adenomas in two brothers, one uncle and an aunt, along with evidence of hyperparathyroidism in their mother and two maternal uncles, is reported as suggesting an autosomal dominant type of inheritance of parathyroid adenomas. The hyperparathyroidism in this family was associated in at least two instances with recurrent pancreatitis. These instances of the association of the two conditions and those in the literature suggest that pancreatitis may at times occur secondary to hyperparathyroidism.

Addendum

The 34 year old male, II–9, was found to have a parathyroid adenoma on reëxploration of the neck. Following excision of the adenoma, the calcium and phosphorus values have returned to normal.

ACKNOWLEDGMENT

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SUMMARIO IN INTERLINGUA

Es reportate le occurrentia de adenomas parathyroide in duo fratres e in duo oncles e un tanta de illes, insimul con evidentia de hyperparathyroidismo in lor matre e un altere oncle de illes. Le factos suggere un typo dominante autosomal de hereditage de adenomas parathyroide.

In al minus duo casos, le hyperparathyroidismo in iste familia esseva associate con pancreatitis recurrente. Le presentia de pancreatitis in solmente alicunes del membros de iste familia de individuos con hyperparathyroidismo e le alleviamento del symptomas de pancreatitis post parathyroidectomia in le duo fratres suggere que pancreatitis es possibilemente relationate in certe casos e de maniera sequential a hyperparathyroidismo.

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OBSERVATIONS ON THE INFLUENCE OF MEDICAL THERAPY ON PORTAL HYPERTENSION IN HEPATIC CIRRHOSIS *†

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CHOICE of medical or surgical therapy for portal hypertension and its manifestations in cirrhosis has been the subject of considerable debate. Proponents for surgical therapy feel that portal hypertension is usually due to irreversible factors and requires operative intervention;[1-3] others believe reversible morphologic and functional alterations contribute to an elevated portal pressure, and advise prolonged medical management.[4-7]

Improved technics for the study of hepatic circulation in man have provided greater objectivity in evaluating response to medical therapy. Portal pressure may be measured indirectly by wedged hepatic vein catheterization,[7-14] percutaneous splenic puncture[15,16] and transesophageal manometric recordings.[17] These studies, coupled with liver biopsy, splenoportography and esophagoscopy, provide a basis for investigating the effects of various therapeutic measures on portal hypertension.[18]

MATERIALS AND METHODS

Fifty patients with biopsy-proved hepatic cirrhosis received a series of biochemical tests, hepatic vein catheterization and splenoportography. Twelve of this group had histologic evidence of mild cirrhosis, 20 had moderate cirrhosis, and 18 had severe cirrhosis by criteria previously outlined.[18] The effects of prolonged rest and dietary therapy, exercise, selected drugs, protein feeding and alterations of intrapleural and intra-abdominal pressure were investigated.

Biochemical tests, histologic studies and wedged hepatic vein pressures were obtained using standard technics.[18] Liver function tests consisted of serum bilirubin, bromsulfalein excretion, serum alkaline phosphatase, serum cholesterol and esters, serum albumin and globulin, the cephalin cholesterol flocculation, serum glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase. Liver biopsy was performed with the Vim-

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Silverman needle without complications. A double lumen catheter was utilized in hepatic vein catheterization. Initial intrasplenic pulp pressures were obtained at the time of splenoportography and repeated without introduction of contrast media for serial observations.

Observations

Wedged and intrasplenic pressures performed within a period of one week of each other showed close agreement in most instances (figure 1). The intrasplenic pulp pressure was considerably higher than the wedged

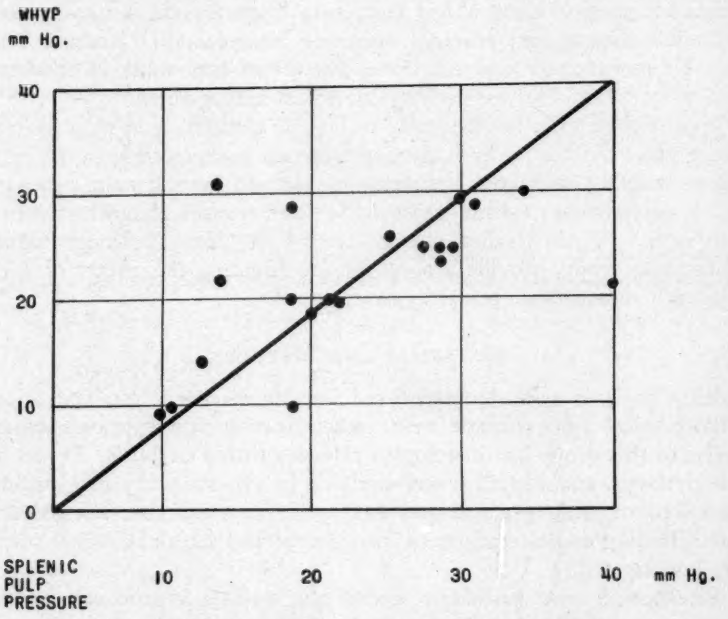

Fig. 1. Correlation of wedged and intrasplenic pressures.

pressure in two patients with complicating portal vein thrombosis, although in one there was evidence of a large, spontaneously occurring splenorenal shunt on splenoportography (figure 2*a*). The intrasplenic pulp pressure was lower than the wedged pressure in three subjects in whom well developed inferior mesenteric collaterals could be demonstrated on splenoportography (figure 2*b*). Both pressures remained elevated in these instances, thereby differing from recordings in extrahepatic causes of portal hypertension, where the wedged pressure remains normal, and cirrhotics with surgically induced portacaval shunts, where the intrasplenic pressure returns to a physiologic level.

FIG. 2. A. Splenoportogram of patient with marked increase in intrasplenic pressure due to a portal vein thrombosis despite presence of a naturally occurring splenorenal shunt. B. Splenoportogram of a patient with reduction in intrasplenic pressure after development of inferior mesenteric collaterals.

There was an inverse relationship between intrasinusoidal pressure and hepatic blood flow. A decrease in estimated portal pressure after medical therapy was usually accompanied by an increase in blood flow. Occasionally the blood flow remained unchanged or decreased with a reduction in pressure. A simultaneous decrease in both pressure and blood flow was attributed to

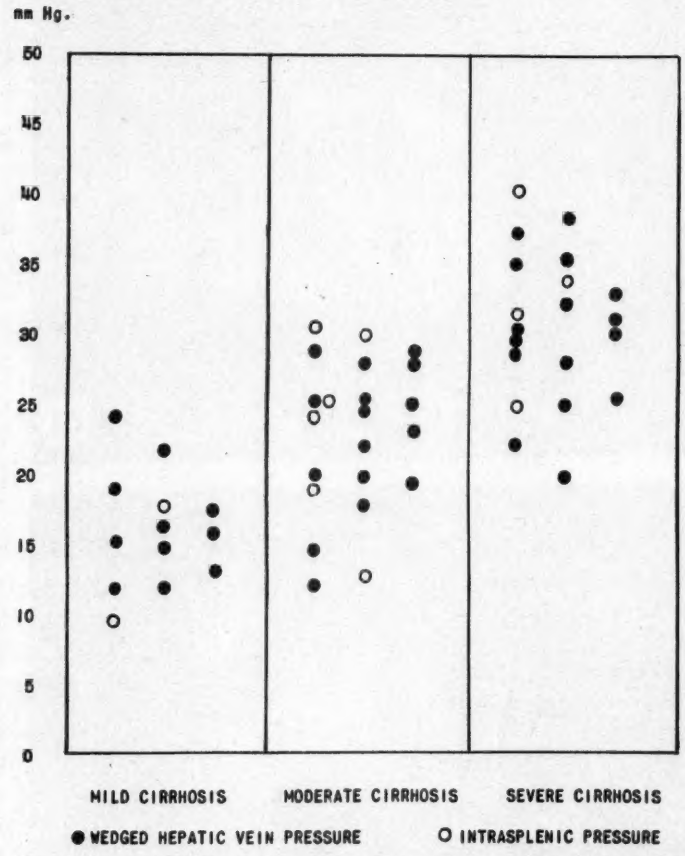

FIG. 3. Correlation of wedged and intrasplenic pulp pressure with histological severity in inactive cirrhosis.

development of collaterals. No correlation could be demonstrated between the wedged or intrasplenic pressures and specific clinical or biochemical abnormalities; however, pressure levels tended to be higher in patients exhibiting clinical signs of portal hypertension. A better correlation was noted between pressure levels and histopathology (figure 3). Nevertheless, it was not possible to predict intrasinusoidal or intrasplenic pressure

from biopsy findings in individual patients. Occasionally there was complete dissociation of clinical, histologic and physiologic findings. Thus in case 7 there were moderate cirrhosis on biopsy, no clinical stigmata of liver disease, esophageal varices on esophagoscopy, a wedged pressure of 35 mm. of Hg, and an estimated hepatic blood flow of 223 ml. per minute.

TABLE 1

Increase in Wedged Hepatic Vein Pressure with Progressive Morphologic Alterations in Cirrhosis

	A Progression of Hepatic Disease after Alcoholism		B Development of Hepatoma in Moderate Cirrhosis	
	Initial Study	4 Months Later	Initial Study	6 Months Later
Clinical Data				
Hepatomegaly (cm.)	4	6	6	7
Splenomegaly (cm.)	1	2	0	0
Spider angiomata	2+	2+	0	
Icterus	0	1+	0	
Fluid retention	1+	2+	0	
Hepatic fetor	0	0	1+	1+
Sensorial changes	0	0	0	0
Esophageal varices	Present	Present	Present	Present
Biochemical Data				
Serum bilirubin (mg./100 c.c.)	0.8	1.3	0	0.1
Sulfobromophthalein retention (%)	11.5	22	Neg.	7
Alkaline phosphatase (B.U.)	5.0	7.0	2.0	2.0
Serum cholesterol (mg./100 c.c.)	300	290	112	134
Cholesterol esters (mg./100 c.c.)	114	94	56	62
Serum albumin (gm./100 c.c.)	3.1	3.0	3.2	3.0
Serum globulin (gm./100 c.c.)	2.9	3.2	2.6	2.6
Cephalin flocculation	2+	3+	1+	1+
Serum glutamic oxalacetic transaminase	—	—	50	42
Serum glutamic pyruvic transaminase	—	—	65	65
Histologic Findings				
Fibrosis	3+	3+	3+	3+
Fat	0	1+	0	0
Regeneration	3+	3+	3+	3+
Bile stasis	0	1+	0	0
Inflammation	1+	2+	2+	2+
Necrosis	0	1+	0	0
Other	0	0	0	Hepatoma
Wedged Hepatic Vein Pressure (mm. Hg)	24	29	28	43

Case 32, with a similar histologic picture accompanied by splenomegaly, ascites and varices, had a wedged pressure of 15 mm. of Hg and hepatic blood flow of 1,100 ml. per minute.

The mean pressure level in patients without fat or inflammation and mild cirrhosis on biopsy was 16 mm. of Hg; it was 23 mm. of Hg in moderate cirrhosis, and 31 mm. of Hg in severe cirrhosis. It was not possible

to correlate the degree of fibrosis, parenchymal cell regeneration, or evidence of intrahepatic arteriovenous shunts with pressure levels.

Serial studies showed an increase in recorded pressures in four alcoholic subjects who returned to alcoholism. This was due to development of fatty metamorphosis in two patients, transition of mild to moderate cirrhosis in one patient, and transition of moderate to severe cirrhosis in one patient.

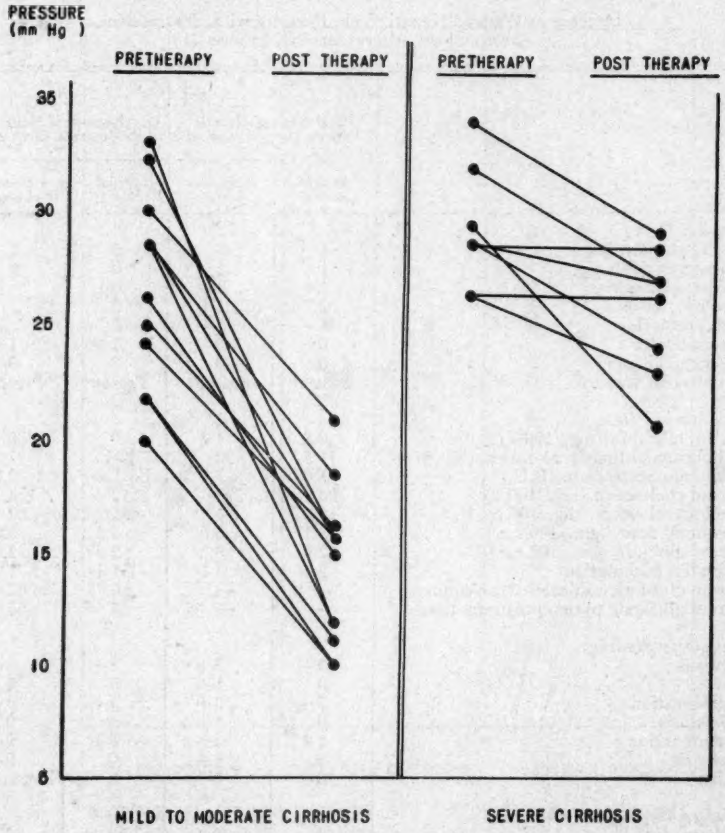

FIG. 4. Effects of medical therapy on estimated portal pressure (serial wedged or splenic pulp pressure) in selected patients with hepatic cirrhosis.

Significant increases in pressure were also noted in a patient with moderate cirrhosis who developed congestive heart failure, and in a patient with severe cirrhosis who developed a hepatoma (table 1).

Estimated portal pressures were reduced in 12 selected patients in whom rest and a diet of 350 gm. of carbohydrate, 125 gm. of protein and 100 gm. of fat for a period of from two to three months were accompanied by removal of fat, decrease in inflammation and fibroblastic activity in the con-

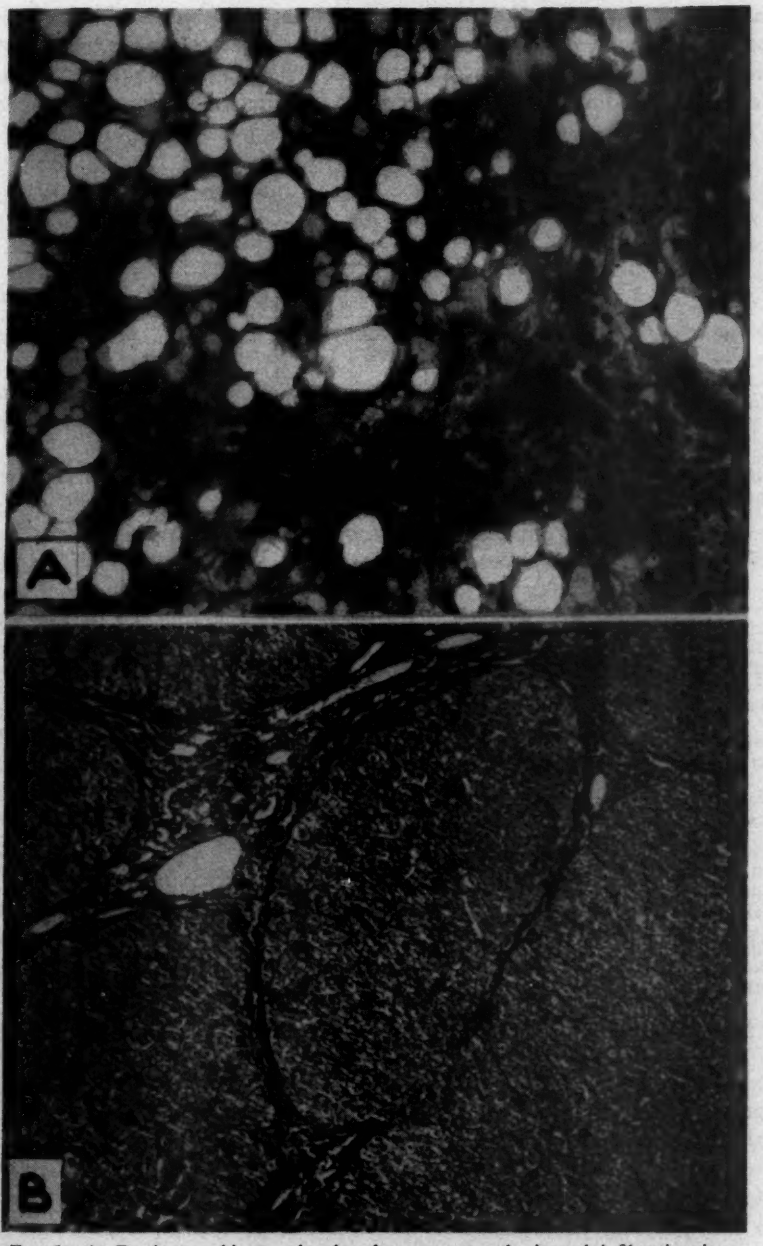

FIG. 5. A. Pretherapy biopsy, showing fatty metamorphosis and infiltration in a patient with moderate cirrhosis and wedged pressure of 28 mm. of Hg. B. Post-therapy biopsy, showing disappearance of fat and decrease of inflammation and a wedged pressure of 11 mm. of Hg.

nective tissue stroma, and disappearance of liver cell necrosis. Five of these patients had mild cirrhosis and seven had moderate cirrhosis (figure 4). The decrease in pressure was accompanied by improvement in clinical and biochemical findings, and an increase in hepatic blood flow. Previously

TABLE 2

Decrease in Wedged Hepatic Vein Pressure with Improvement of Cirrhosis

	A Mild Cirrhosis with Fatty Metamorphosis		*B* Moderate Cirrhosis with Fat and Inflammation		*C* Severe Cirrhosis with Inflammation	
	Initial	After 2 Mos. Therapy	Initial	After 2 Mos. Therapy	Initial	After 6 Mos. Therapy
Clinical Data						
Hepatomegaly (cm.)	4	2	6	2	7	6
Splenomegaly (cm.)	0	0	0	0	0	0
Spider angiomata	0	0	2+	0	2+	1+
Icterus	0	0	0	0	0	0
Fluid retention	1+	0	2+	0	3+	0
Hepatic fetor	0	0	0	0	0	0
Sensorial changes	0	0	Present	Absent	Present	Absent
Esophageal varices	Absent	Absent	Present	Absent	Present	Absent
Biochemical Data						
Serum bilirubin (mg./100 c.c.)	0.0	0	1.8	0.1	1.6	0
Sulfobromophthalein retention (%)	0	0	42	5	19.5	19
Alkaline phosphatase (R.U.)	—	—	14.8	4.7	4.3	2.5
Serum cholesterol (mg./100 c.c.)	123	180	261	270	128	164
Cholesterol esters (mg./100 c.c.)	54	47	141	150	60	84
Serum albumin (gm./100 c.c.)	3.2	3.5	2.3	4.1	1.3	2.8
Serum globulin (gm./100 c.c.)	1.7	2.1	1.9	1.6	3.7	3.3
Cephalin flocculation	2+	0	neg.	neg.	3+	2+
Serum glutamic oxalacetic transaminase (units)	46	46	42	32	42	54
Serum glutamic pyruvic transaminase (units)	54	25	14	17	15	46
Histologic Findings						
Fibrosis	1+	1+	2+	3+	3+	3+
Fibroblastic activity	1+	1+	2+	1+	2+	1+
Fat	3+	0	1+	0	1+	0
Regeneration	2+	2+	3+	0	3+	3+
Bile stasis	0	0	0	0	0	0
Necrosis	1+	0	2+	1+	2+	2+
Other	0	0	1+	0	0	0
Wedged Hepatic Vein Pressure (mm. Hg)	32	10	28	11	27	21

demonstrated esophageal varices were no longer evident in three of this group.

There was an average decrease in estimated portal pressure of 10 mm. of Hg with removal of fat from biopsy specimens. Lesser falls were noted in subjects with mild degrees of fat in whom the principal histologic evidence of improvement was a decrease in inflammation and fibroblastic

activity in the connective tissue stroma. The most pronounced fall in pressure occurred in patients with a combination of steatosis and connective tissue activity (figure 5, table 2).

Eight patients with severe cirrhosis where there was complete distortion of the lobular pattern, marked fibrosis and well developed parenchymal cell nodules [18] showed maintained elevation of recorded pressures despite prolonged therapy for periods of up to one year. Repeat studies usually showed a difference of 3 to 6 mm. of Hg (figure 4), considered to be insignificant or within the range of error. Five of this group had active inflammation in the connective tissue stroma, and three had no histologic evidence of activity. Intrasplenic pulp pressure obtained after a period of medical therapy in this group was lower than the wedged pressure in two of the patients with active cirrhosis and in one with inactive cirrhosis. Splenoportography showed collaterals without evidence of esophageal varices in these patients.

Pharmacologic studies showed marked variation of wedged and free hepatic vein pressures in response to both vasopressor and vasodilator agents. One third of the subjects tested showed no significant change in pressure despite alterations of cardiac output and peripheral resistance. Least response was noted in patients with histologic evidence of severe cirrhosis and numerous extrahepatic collaterals on splenoportography.

Epinephrine and Levophed produced a pronounced rise in intrasinusoidal pressure in selected subjects. This demonstration was of practical significance in a patient who bled from esophageal varices after administration of epinephrine for control of an episode of bronchial asthma. There was an increase in wedged pressure from 25 to 36 mm. of Hg following administration of 0.3 c.c. of the drug subcutaneously. Although pituitrin, ouabain and hexamethonium bromide produced a significant decrease in wedged pressure in some patients, the reduction was transitory and did not appear to be sufficient to prevent or control varix hemorrhage from an increase in hydrostatic pressure in esophageal collaterals.

A five-minute period of vigorous exercise employing a standard exerciser caused an increase in wedged pressure of from 5 to 10 mm. of Hg in several patients; however, most of the subjects had little change in wedged pressure following physical exertion. Protein feeding, previously reported to cause a pronounced rise in intrasinusoidal pressure,[21] produced no significant alteration in wedged pressure under the conditions of our studies. After ingestion of 60 gm. of protein in the form of meat, there was little change in recorded pressure over a four-hour interval in seven patients, although the hepatic venous ammonium often increased markedly as a reflection of protein catabolism in those with severe liver damage (figure 6).

An increase in intrapleural and intra-abdominal pressure following cough or the Valsalva maneuver, and rises in intra-abdominal pressure due to ascites, had a marked effect on the intrasinusoidal pressure. Severe bouts

of coughing increased a normal wedged pressure to hypertensive ranges and frequently doubled an already elevated pressure (figure 7*a*). The Valsalva maneuver produced a sustained increase in intrasinusoidal pressure (figure 7*b*). Effects of ascites on wedged pressure were demonstrated by serial

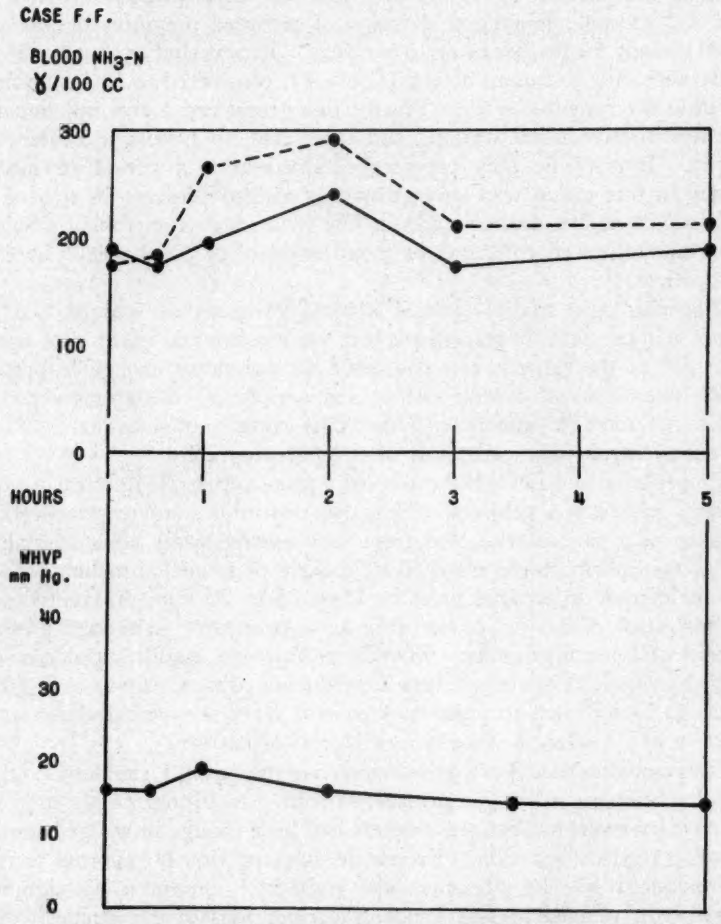

FIG. 6. Serial wedged pressure and blood ammonium levels after ingestion of 60 gm. of protein, showing no significant alterations of pressure. The dotted line represents the hepatic venous ammonium, and the solid line arterial ammonium.

studies of wedged pressures during removal of ascitic fluid by paracentesis. Ascites increased intrasinusoidal pressure, and the resulting splanchnic pooling of blood contributed to the further accumulation of peritoneal fluid by its effect on hydrostatic pressure and elaboration of salt-retaining hormones.[15] Mobilization of ascites which followed improvement of hepatic

reserve; use of an intensive diuretic regimen consisting of sodium restriction, potassium chloride, mercurials and chlorthiazide; and adrenal suppression with Medrol in patients refractory to diuretics, were accompanied by a reduction of intrasinusoidal pressure. The degree of increase of the wedged pressure in ascites was not necessarily related to the amount of peritoneal fluid, and could be approximated by subtracting the difference of the supradiaphragmatic and abdominal vena caval pressures from recorded wedged

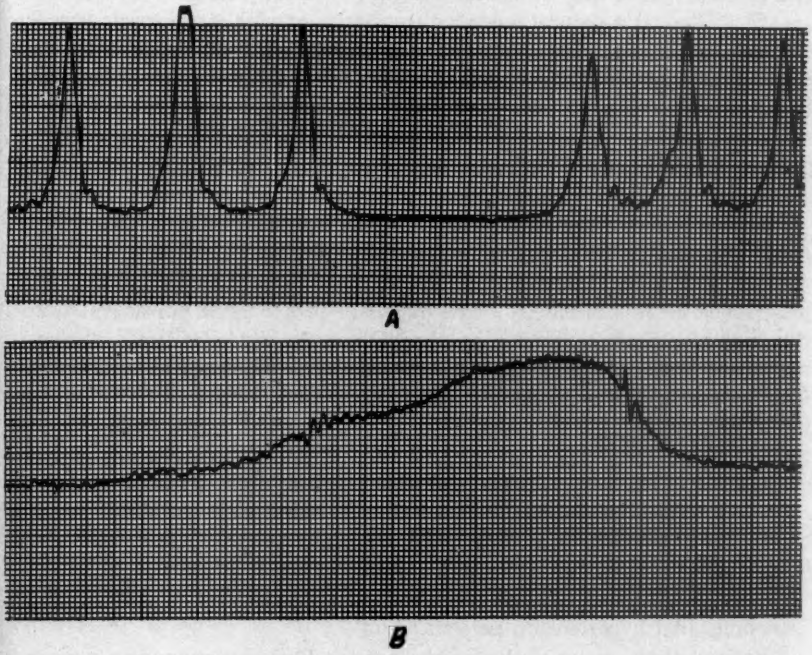

FIG. 7. A. Effects of cough on the wedged hepatic vein pressure. B. Effects of the Valsalva maneuver on wedged hepatic vein pressure.

pressure.[16] An increase in pressure in the inferior vena cava was occasionally seen in the absence of ascites, presumably due to compression of this vessel during its passage through a distorted liver bed.

DISCUSSION

The demonstrated validity and simplicity of circulatory studies of the liver, and the evidence that an elevated portal pressure may be influenced by spontaneously developed collaterals, changes in histopathology, drug therapy and physiologic alterations, permit the clinician to employ a more rational program in the treatment of portal hypertension in cirrhosis. The lack of correlation of physiologic studies with clinical, biochemical and

histologic findings reëmphasizes the need for a composite approach to liver disease.[18] All patients with chronic hepatic disease should be suspected of having portal hypertension, its degree and significance requiring circulatory studies for proper evaluation.

A combination of wedged hepatic vein pressure, intrasplenic pulp pressure and splenoportography is desirable to evaluate the presence and significance of spontaneous pressure adjustments in cirrhosis. Esophagoscopy and barium studies may be unreliable and not reflect changes in portal pressure.[22] There is a natural tendency to compensate for intrahepatic vascular blockade as evidenced by the lowering of intrasplenic pressure in some patients with numerous extrahepatic collaterals.[18] No further therapy may be required in patients who develop this "natural shunt." Occasionally these individuals will exhibit ammonium intoxication following meat ingestion, and require protein restriction or use of antibiotics to prevent hyperammoniumemia.[23, 24]

Continuation of the pathogenetic mechanism leading to cirrhosis is usually responsible for eventual rupture of esophageal varices, as neither morphologic changes nor portal hypertension appears to be spontaneously progressive in this disease.[25] The merits of prophylactic portacaval shunts in patients with asymptomatic esophageal varices can be critically evaluated only after excluding subjects with reversible morphologic alterations who may respond to a prolonged medical regimen. Indications for surgical portal decompression are clearer with portal hypertension and bleeding esophageal varices.[26, 27] In our experience, 20% of patients with moderate cirrhosis and bleeding varices have survived five years without recurrence on adequate medical therapy.[18] Nevertheless, surgical portal decompression represents a lifesaving procedure and is advocated for acceptable risk patients in this category. An effective end-to-side portacaval shunt may be followed by a significant reduction in wedged pressure;[28] however, in most instances, intrasinusoidal hypertension persists.[7]

Patients with severe cirrhosis who are not likely to respond to a medical regimen are also poorer candidates for surgical therapy. A program which avoids the changes in portal pressure incident to coughing, straining at the stool, and vasoconstrictor drugs, coupled with treatment of the peptic acid factor[29] and control of hemostatic abnormalities, may prevent recurrent hemorrhage for an indefinite period. None of the vasodilators studied to date appears to be of value in reducing portal pressure for prolonged periods.

Portal hypertension associated with ascites refractory to a medical regimen for cirrhosis represents a most difficult therapeutic problem. Secondary hyperaldosteronism appears to be largely responsible for the increased tubular reabsorption of sodium characteristic of this state.[30] Increased intrasinusoidal pressure causes pooling of blood in the splanchnic area and contributes to a reduction in effective circulatory volume and an expansion of extracellular volume, both of which are stimuli for further

elaboration of aldosterone.[30, 31] Although paracentesis may reduce intrasinusoidal pressure and thereby temporarily interrupt elaboration of aldosterone, its effect is only transitory and contributes to debility by decreasing circulating protein and further reducing effective circulatory volume. In patients refractory to a medical regimen, portacaval shunting currently appears to be the most physiologic surgical approach, and resulting mobilization of ascites may be accompanied by a reduction in wedged pressure and sodium diuresis.[7]

Summary and Conclusions

1. Serial studies of wedged hepatic vein and intrasplenic pulp pressures correlated with histopathology in hepatic cirrhosis indicate that fatty metamorphosis, inflammation and liver cell necrosis contribute to portal hypertension in this disease. Medical therapy may cause reduction or disappearance of an elevated portal pressure in these instances.

2. Medical management usually has no effect on an elevated wedged or splenic pulp pressure primarily due to nodular regeneration of liver cells, intrahepatic vascular shunts and inactive fibrous connective tissue. A reduction in intrasplenic (portal) pressure may occur with spontaneous development of collaterals although the intrasinusoidal pressure remains unchanged.

3. Vasoconstrictor drugs, cough, the Valsalva maneuver and ascites may produce a marked increase in portal pressure. In cirrhosis with esophageal varices such increments should be avoided.

4. Circulatory studies are important in hepatic cirrhosis with portal hypertension to establish the level of portal pressure, determine the effectiveness of medical therapy and evaluate the need to resort to surgical procedures. They have furnished additional information on the natural history of portal hypertension and have provided a more objective method of assessing various therapeutic measures.

Summario in Interlingua

Cinquanta patientes con cirrhosis hepatic, provate per biopsia, recipeva un serie de tests biochimic, catheterismo de vena hepatic, e splenoportographia pro evalutar le influentia que le therapia medical exerce in iste morbo super le hypertension portal. Le determination simultanee de pression cuneate e de pression intrasplenic monstrava un intime accordo in le majoritate del casos. Le pression de pulpa intrasplenic esseva considerabilemente plus alte que le pression cuneate in duo patientes con le complication de thrombosis de vena portal. Illo esseva plus basse que le pression cuneate in tres subjectos in qui le splenoportographia demonstrava le presentia de ben-disveloppate collaterales infero-mesenteric. Le nivellos medie del pression esseva 16 mm de Hg in patientes con leve grados de cirrhosis biopticamente evalutate, 23 mm de Hg in patientes con moderate grados de cirrhosis, e 31 mm de Hg in patientes con cirrhosis sever.

Studios serial del pression cuneate de vena hepatic e del pression de pulpa intrasplenic indicava que in iste morbo metamorphosis grassiose, inflammation, e necrose de cellulas hepatic contribue al promotion del hypertension portal. In tal casos, le

therapia medical pote effectuar un reduction o disparition del hypertension portal. Usualmente le tractamento medical habeva nulle effecto super le elevation del pression cuneate o del pression de pulpa splenic, primarimente causate per regeneration nodular del cellulas hepatic, derivationes de vasos intrahepatic e inactivitate de histo conjunctive fibrose. Un reduction del pression intrasplenic (portal) pote occurrer con le disveloppamento spontanee de vasos collateral, ben que le pression intrasinusoide remane non-alterate.

Drogas vasoconstrictori, tusse, le manovra de Valsalva, e ascites pote producer un marcate augmento del pression portal. Un programma therapeutic que evita alterationes del pression portal in consequentia de iste mechanismos, associate con le tractamento del factor de ulcere peptic e del anormalitates hemostatic, pote succeder a prevenir hemorrhagias ab varices esophagee durante un periodo indefinite. Exercitio e alimentation de proteina habeva nulle effecto significative super le pression portal. Pituitrina posterior, ouabaina, e bromuro de hexamethonio causava transiente e usualmente pauco significative reductiones del pression portal.

Es concludite que studios del circulation es importante in cirrhosis hepatic que es associate con hypertension portal. Illos servi a establir le nivello del pression portal, a evalutar varie mesuras therapeutic que es recommendate pro le tractamento, a determinar le efficacia de un prolongate therapia medical in le patiente individual, e a judicar le necessitate de recurrer a methodos chirurgic.

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INTERPRETATION OF HEMATOLOGIC AND SEROLOGIC FINDINGS IN THE DIAGNOSIS OF INFECTIOUS MONONUCLEOSIS*

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ARTICLES stressing certain rare and preternatural manifestations of infectious mononucleosis continue to occupy a prominent place in the literature of this disease. It is noteworthy that atypical clinical features have not been the only atypical findings in many of these cases. I have been puzzled by cases that have failed to show a lymphocytosis. For example, although heterophil tests were positive in a case recently reported in a four year old girl with severe central nervous system involvement, other findings included a neutrophilia of 93%, no abnormal lymphocytes at any time during the illness, and none of the usual clinical manifestations of infectious mononucleosis.[1]

In my own experience the differential counts of patients with this disease have regularly been characterized by a lymphocytosis. In all cases the diagnosis was further substantiated by high atypical lymphocyte counts and by heterophil antibody titers of 1:56 or greater, as well as by clinical manifestations common to infectious mononucleosis. These observations embrace 600 carefully studied cases, for the most part seen in a university population. The lymphocytosis has not been a transient finding, but present day after day during the acute phase and early convalescence. It is apparent that a willingness to make the diagnosis in the absence of typical hematologic findings will yield many examples of infectious mononucleosis with bizarre clinical features. As will be shown later, a positive heterophil test may be encountered in other situations. In the absence of straightforward clinical features, it is of the utmost importance that both the serologic and the hematologic criteria be fully satisfied before making the diagnosis of infectious mononucleosis.[2, 3]

As a consequence of the wide range of blood pictures reported in infectious mononucleosis, minimal hematologic findings diagnostic of this disease have not been agreed upon. It is usually stated that there should be a lymphocytosis of more than 50%, and that atypical lymphocytes should be present. The indefinite implications of such a finding would seldom prove helpful, certainly never diagnostic. It is the main purpose of this article to present data helping to define changes in the differential white cell count acceptable for the diagnosis of infectious mononucleosis. The evaluation

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of a positive heterophil test in the absence of diagnostic hematologic findings is discussed. A heretofore unreported finding, a nonspecific anamnestic reaction of heterophil antibodies occurring during an attack of atypical pneumonia, is illustrated by a case report.

The Lymphocytes

From the laboratory standpoint, the basic screening procedure in the diagnosis of infectious mononucleosis is the identification of atypical lymphocytes. The nonspecific nature of these cells is well known, and has no doubt contributed to a willingness to regard their presence as unessential. Hoagland, who has made a careful study of many facets of this disease, has stressed that one never sees a patient who has clinical and serologic manifestations of infectious mononucleosis who does not also have characteristic blood cell changes.[4] My own findings indicate that atypical lymphocytes make such a substantial contribution to the total white cell count as to be almost pathognomonic of infectious mononucleosis. It will not be amiss to reëmphasize that blood smears as prepared in the average laboratory for routine differential counts are unsatisfactory for the identification of atypical lymphocytes. Recognition of these cells is made much easier when blood smears are made about one-half the usual thickness.

In well stained thin smears made during the early part of the illness the atypical lymphocytes are quite easily identified. It is during the latter part of the illness that recognition frequently becomes difficult. At this time a few cells with unimpressive shallow nuclear depressions or irregularities, among a monotonous array of normal lymphocytes, may be the only residuum of many large cells with variegated nuclear patterns present several weeks earlier. Sometimes cytoplasmic inclusions increase and many cells seem to be transitional forms between the lymphocyte and the monocyte. Not infrequently when a differential white cell count is attempted during the late convalescent period, differentiation of the mononuclear cells becomes so arbitrary as to render the figures worthless.

The uniform hematologic features of this disease will be appreciated and utilized to good advantage when two simple practices are followed. Briefly, interpretation of hematologic findings should be based on well stained smears with little overlapping of cells, made during the febrile period of the disease. Blood smears prepared during the early and midfebrile periods of the illness are especially worth while because they contain atypical lymphocytes of the most florid patterns. Later in the illness it will not be possible to differentiate atypical lymphocytes from other mononuclear cells with the same degree of certainty.

Figure 1 shows the range of atypical lymphocyte percentages in 200 patients with infectious mononucleosis. The patients selected for inclusion here were seen early in the illness and were under continuous hospitalization. None was receiving antibiotic, sulfonamide or corticosteroid therapy.

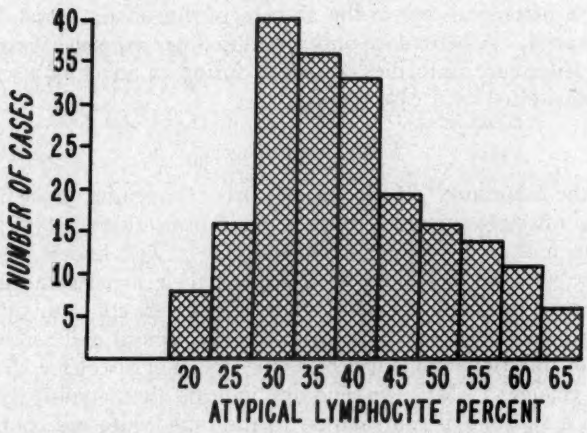

FIG. 1. Atypical lymphocyte percentages, arranged in 5% class intervals, in 200 cases of infectious mononucleosis.

Total and differential white cell counts were done daily during the early part of the illness while symptoms were increasing in severity. The counts recorded were made the day following the initial fever peak, usually from four to six days after the patient entered the hospital. This reference point was selected arbitrarily and does not imply that the atypical lymphocyte count is highest at this exact time. Actually, counts of the same order were present daily for one or two weeks, depending upon the severity of the illness. The percentage range was from 20 to 67, the average 41.3. All cases tested had 20% or more atypical lymphocytes; 96% had 25% or

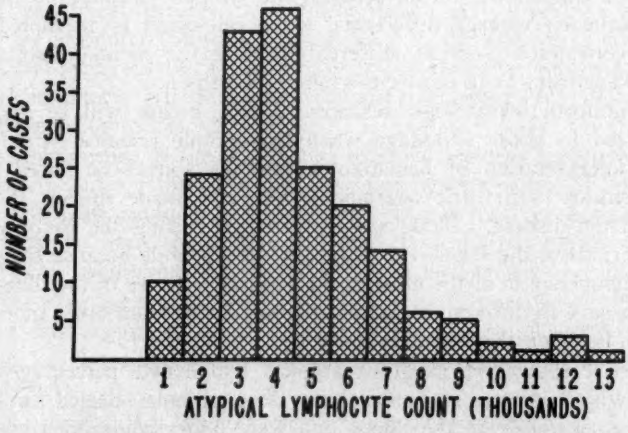

FIG. 2. Absolute atypical lymphocyte counts, class intervals of 1,000, present in 200 cases of infectious mononucleosis.

more of these cells. These observations suggest that only in rare instances would infectious mononucleosis be accompanied by less than 20% atypical lymphocytes during the high febrile phase.

Figure 2 shows the absolute atypical lymphocyte counts for the same group. The range of the total white counts was from 5,100 to 26,500 cells; 71% had a leukocytosis. The atypical lymphocyte range was from 1,400 to 13,500 cells; the average was 4,884. Of the 34 cases (first 2 columns) showing less than 3,000 atypical lymphocytes, only seven had a leukocytosis. All total counts of 11,500 and over had at least 3,000 atypical lymphocytes.

A number of virus infections, especially the exanthemata, occasionally have blood smears showing up to 1,500 young mononuclear cells. Many

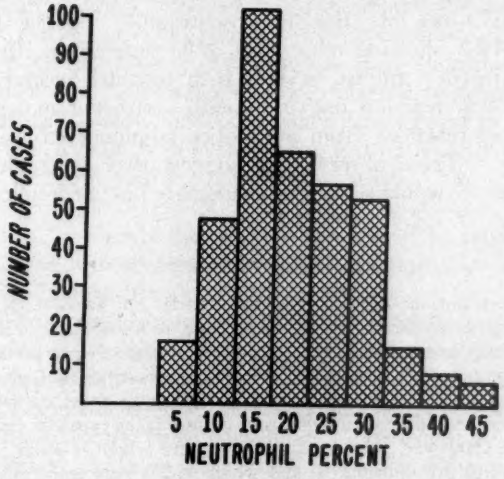

FIG. 3. Neutrophil percentages, arranged in 5% class intervals, present in 370 cases of infectious mononucleosis.

of these cells are young monocytes and plasma cells. Counts of this order are short-lived, often present in an isolated count, and almost never lasting over three days. In infectious mononucleosis the atypical lymphocyte counts do not fall off precipitously once the maximal level is reached. Even in cases developing the smallest number of atypical lymphocytes, these levels are sustained for a week or longer.

THE NEUTROPHILS

Because of the accuracy with which neutrophils can be identified, these cells were studied separately. Inspection of the records of the 200 patients seen early in the illness and having particularly complete hematologic study (figure 1) revealed the following: In only one instance was the neutrophil count lowest early in the disease. In some the lowest count coincided with

the fever peak. Most cases, however, showed the lowest neutrophil percentage a day or two before leaving the hospital, about the time when the temperature returned to normal. The 370 cases (figure 3) are composed of the previous group of 200 plus an additional 170 cases. The patients in the latter group did not come under our care until the febrile period had been established. Because of the tendency for the lowest neutrophil count to occur late in the illness, the counts recorded at the end of the febrile period were used in compiling figure 3. The relative value of neutrophil counts late in the illness is peculiarly enhanced because of the uncertainties in identification of mononuclear cells at this stage of the disease.

The average neutrophil percentage (figure 3) was 22.2. The range was from 6 to 49%. It can be seen that all cases tested had less than 50% neutrophils; 96% had less than 40% neutrophils. In the 14 cases (last two columns, 4%) showing more than 39% neutrophils, five had moderately severe Vincent's angina, several with tonsillar ulceration. Another had a severe local reaction due to recently extracted molar teeth. Two others had drug reactions from antibiotics administered prior to coming under our care. These observations suggest that neutrophil percentages consistently over 49 would seldom be encountered in uncomplicated infectious mononucleosis.

More Precise Predictions *

Since the distributions are not only non-normal but asymmetric, the values for means and standard deviations would have little meaning here. Nevertheless, the results of this study are susceptible to a precise statistical interpretation. Observations on the percentages of cells studied are chance quantities, and as such have probability distributions. If fittings of frequency curves to these distributions were to be attempted, there would arise the question of just what types of curves to fit. For our purpose here, however, there exists a procedure which is valid regardless of the way these quantities are distributed, and which yields very good results. This procedure consists of specifying what are known as one-sided distribution-free tolerance limits. Thus:

1. We can state with 99.9% confidence (odds of 999 to one) that at least 96.6% of all future patients with infectious mononucleosis will have atypical lymphocyte counts of 20% or higher, or absolute counts of 1,400 or higher.

2. We can state with 99.9% confidence that at least 98.2% of all future patients with infectious mononucleosis will have neutrophil counts of 49% or less.

These statements are based on the following formula,[5]

$$1 - \left(\frac{y}{100}\right)^n = \frac{x}{100}$$

where n is the sample size (200 for the first statement and 370 for the second statement), x the confidence measured in per cent, and y the per cent of future patients tested. Notice that x and y are in an inverse relationship—that is to say, for higher confidence our statements would apply to smaller percentages of future patients, or alternately, for larger percentages of future patients the confidence must be lowered.

* I am indebted to Professor R. F. Tate, Department of Mathematics, University of Washington, for this summary.

The Heterophil Test

In general, a differential absorption formula showing little or no absorption of the antibody by guinea pig antigen and complete absorption by beef cell antigen is diagnostic of infectious mononucleosis. Minimal serologic evidence needed to make the diagnosis is as follows: with unabsorbed serum, a sheep cell agglutination titer of 1:56; after absorption of the serum with guinea pig kidney, a titer of 1:28, at least 1:14. After absorption with beef cell antigen, no agglutination of sheep cells should occur. Without a completely typical clinical syndrome, a differential absorption test of this low order of specificity should be rechecked for confirmation. Readings are made macroscopically after two hours' incubation at room temperature.

A practical point seldom considered in discussions of the heterophil test is the question of reading after overnight refrigeration versus incubation at room temperature for two hours. The original Paul-Bunnell technic published in 1932 called for readings made after overnight refrigeration of the tubes.[6] This practice has been abandoned, since it may result in falsely high titers. Nevertheless, a recently published large text on laboratory diagnosis still retains this recommendation. Davidsohn in 1937, in outlining the principles for the serologic diagnosis, recommended that readings be made at room temperature.[7] This is the method that should be followed. It is unfortunate that some authors have stated that the figures for Davidsohn's method refer to readings made after refrigeration.

In many straightforward examples of infectious mononucleosis the titers after absorption with guinea pig antigen are reported as several tubes below that with unabsorbed serum. Aside from the possibility that some Forssman's or infectious mononucleosis antibody has actually been removed, there is at least one technical factor to be considered. For example, I have seen extremely coarse guinea pig saline mixtures which make it difficult to secure a representative specimen of the preparation. This results when a coarse antigen particle becomes lodged in the tip of the pipet used to draw up the mixture, allowing only saline and very small antigen particles to be drawn into the pipet. This distortion of the normal 1:4, solid-saline ratio in favor of the latter results in lower final titers because of excessive dilution of the serum. This explanation will become obvious when it is discovered that the laboratory bottle containing the guinea pig antigen contains a heavy layer of solid material with only a few drops of diluent remaining. Using a finely divided guinea pig mixture, I usually find titers one tube lower than with the unabsorbed serum—less frequently, the same or two tubes lower. With careful technic, titers more than three tubes lower indicate other than infectious mononucleosis-type antibody. In my experience, beef cell antigen removes all the infectious mononucleosis heterophil antibodies. Extremely high titers may prove an exception.[8]

Because of the cumbersome technic of the complete differential absorption test, short cuts are sometimes adopted. A common practice is to forego

absorption with the beef cell antigen and rely solely upon the inability of the guinea pig kidney to remove substantial amounts of antibody to clinch the presence of infectious mononucleosis-type antibody. The shortcomings of such a policy are illustrated by the following case.

Case Records

Case 1. In 1949 the author treated a 25 year old male with posterior cervical adenopathy. No fever or pharyngitis was present. The total and differential white cell counts were entirely normal. A differential absorption test during the second week of illness was: presumptive titer, 1:112; after guinea pig absorption, 1:28; after beef cell absorption, 1:112. The failure of the beef antigen to remove the antibodies, noted in three separate specimens, clearly showed they were not infectious mononucleosis type. Had this portion of the test been neglected, an interpretation based on the presumptive and guinea pig titers alone would surely have resulted in the diagnosis of infectious mononucleosis. After several weeks, jaundice and hepatosplenomegaly appeared. The patient died two and one-half years later of Hodgkin's disease after several exacerbations and remissions. After the initial few weeks of the illness no sheep cell agglutinins were ever found. No lymphocytosis or atypical lymphocytes ever occurred. In view of the gross clinical and laboratory deficiencies it seems extremely unlikely that this patient had infectious mononucleosis at this period. Testing of serum after absorption with beef antigen for its ability to agglutinate sheep cells is a decisive step in reaching the correct diagnosis.

It will be apparent from what follows that much of the information on the incidence of positive heterophil tests in other diseases is inconclusive because of failure to follow the standard technic, or failure to do complete differential absorption tests when essential. In the opinion of the writer, differential absorption tests are unessential when the presumptive titer is 1:56 or over as long as there is a typical hematologic and clinical picture. This means a febrile, posterior cervical adenopathy, pharyngotonsillitis and splenomegaly syndrome.[9] Absence of either of the first two signs—better, any of the first three—or the appearance of some atypical feature makes it advisable to do a complete absorption test regardless of the presumptive titer. It cannot be emphasized too strongly that significant hematologic deficiencies and alterations in this basic clinical picture, rather than titer levels per se, are the more important considerations in establishing the necessity for a differential absorption test.

In a study of 141 cases Schultz found 57 with heterophil titers of 1:56 or over.[10] These included Hodgkin's disease, sarcoma, polycythemia, agranulocytosis, myeloid, lymphatic and monocytic leukemia, and tuberculosis. Of special interest was the finding of positive heterophil tests in over 65% of both the terminal and the completely arrested cases of tuberculosis. It is possible that the large percentage of positive tests was due to the fact that readings were made after overnight refrigeration of the tubes. Apparently no differential absorption tests were performed.

In another large study Goldman found positive heterophil tests (titers 1:80 and over) in 46 cases (10%) of 458 patients with miscellaneous dis-

orders, and in four patients (7.3%) of 55 cases of Hodgkin's disease, leukemia and lymphomatous disease.[11] Readings were made after refrigeration of the tubes. This study failed to support the common concept of abnormally high titers of heterophil antibodies in lymphomatous diseases. In only three cases in this large series were heterophil titers 1:80 or greater after guinea pig absorption. This extensive survey establishes the occurrence of positive heterophil tests in from 7 to 10% of general disease states. Apparently the beef cell absorption technic was not done.

A much higher incidence of positive heterophil tests, 1:56 and over, was reported by Southam in a similar group of cases.[12] Of 94 patients with acute leukemia, 45% had positive tests. Of 37 patients with other types of neoplastic diseases, excluding chronic leukemia and lymphosarcoma, 35% had positive tests. In all but one instance, a case of hypernephroma, guinea pig antigen removed all or almost all of the sheep cell agglutinins. Readings were made after overnight refrigeration of the tubes, and beef cell titers were not reported.

Carpenter reported two cases of monocytic leukemia, both with heterophil tests of 1:896; however, complete differential absorption tests indicated that infectious mononucleosis-type heterophil antibodies were absent.[13] Kaufman reported a case of Hodgkin's disease in a 30 year old male.[14] Heterophil titers on unabsorbed, guinea pig and beef cell serums were 1:112, 1:28 and negative, respectively. Nine months later the titers were 1:224, negative and 1:56. While the original differential absorption formula was positive for infectious mononucleosis, the failure of the beef cell antigen to remove the antibody nine months later, as well as complete absorption by the guinea pig antigen, points to normal Forssman-type antibody.

Massey reported an unusual example of acute infectious mononucleosis and Hodgkin's disease occurring simultaneously.[15] On three separate occasions, none to moderate amounts of antibody were removed by the guinea pig antigen, consistent with the behavior of infectious mononucleosis heterophil antibodies. While titers after absorption with beef cells were not reported, the finding of 68% atypical lymphocytes strongly supports the view that infectious mononucleosis and Hodgkin's disease existed simultaneously. In this interesting case with highly typical laboratory findings, it would appear logical to attribute the presence of heterophil antibodies to infectious mononucleosis rather than to Hodgkin's disease. Feldman reported lymphatic leukemia and infectious mononucleosis coexisting in an 18 year old white male.[16] Early in the illness the cells were those found in infectious mononucleosis, and a complete differential absorption test was positive. Later in the illness the heterophil test became negative.

In review, heterophil tests positive in titers of 1:56 or higher on unabsorbed serum are not uncommon in a variety of disease states. After absorption with guinea pig antigen, however, only a few cases show significant antibody levels. Failure to make readings at room temperature

and failure to complete all three stages of the differential absorption test have detracted from the value of several extensive studies. Conclusive evidence often depends as much upon the results of the commonly omitted beef antigen procedure as upon the first two stages of the test.

The Positive Heterophil Test with Normal Differential Counts

Additional observations have always demonstrated high atypical lymphocyte counts in patients with infectious mononucleosis. There has been no evidence that a normal or near-normal differential white cell count could persist during the acute phase of this disease. The following observations afford one explanation of the paradox of a positive heterophil test with normal differential counts reported in a number of cases of atypical infectious mononucleosis.

Case 2. On the sixth day of illness a 29 year old white male had a white blood cell count of 6,800, 67% neutrophils, 19% lymphocytes, 13% monocytes and 1% eosinophils. The heterophil titer was positive, 1:112. On the ninth day the titer was 1:224, positive 1:112 after absorption with guinea pig kidney, and negative for heterophil antibodies after absorption with beef cells. There was a low grade febrile course with a nonproductive cough, and x-rays showed a pneumonitis of the left lower lobe. Recovery was prompt, with heterophil titers falling quickly and cold agglutinin titers rising significantly. Thirteen weeks earlier this patient had had typical anginose infectious mononucleosis, with a heterophil titer of 1:896. The titer 76 days later was 1:28; this was 12 days prior to the titer of 1:112 obtained on the sixth day of the new illness. The patient was completely well and working during the 11 weeks between the illnesses. Noteworthy features of the second illness were repeatedly normal total and differential white cell counts, and absence of all the usual clinical manifestations of infectious mononucleosis.

Heretofore, anamnestic reactions of heterophil antibodies in significant titers have not been reported.[17] Depending upon the information available, the second illness might have been called atypical infectious mononucleosis, infectious mononucleosis with atypical pneumonia, or recurrent infectious mononucleosis. I interpret this transient elevation of heterophil antibodies as evidence of a nonspecific anamnestic reaction related to the atypical pneumonia. Similar findings have been present in three other individuals with undifferentiated upper respiratory infections occurring after an attack of infectious mononucleosis. In a recent case, significant elevations of heterophil antibodies occurred during each of two separate episodes of group A streptococcic tonsillitis and peritonsillar abscess in a patient I had treated for severe anginose infectious mononucleosis exactly one year before. It should be noted that these findings are exceptions rather than the rule. Apparently only a very few patients show a resurgence of heterophil antibodies at the time of subsequent infectious diseases.

A more common explanation for an isolated positive heterophil test depends upon the presence of antibodies persisting from an earlier attack of

infectious mononucleosis. In a given case there is no way of predicting at what levels, or for how long, antibodies persist. It has not been my policy to follow the titer of heterophil antibodies month after month once a significant downward trend has been established. However, my records show that some asymptomatic patients have titers of up to 1:224 five months after a slight or moderately severe attack of infectious mononucleosis. Furthermore, at the University of Washington Health Center we find a substantial number of students with infectious mononucleosis and symptomatology so minor that it is doubtful whether they would ever have sought private medical care. Most individuals would look upon their illness as a "bad cold" or the "flu," and it would be quickly forgotten. Should a positive heterophil test be discovered in connection with a subsequent illness, the true source of the antibodies would probably be unsuspected.

The heterophil test must be interpreted in the light of all events bearing on a given illness. Even a positive differential absorption test for infectious mononucleosis heterophil antibodies merely establishes their presence. This should be looked upon as an accessory finding, since the agglutinins may have lingered from a recent unrecognized attack of infectious mononucleosis, or have been recalled, as in the case described. In my experience, atypical lymphocyte counts of the order described in this paper are present only during acute infectious mononucleosis, but not when a resurgence of heterophil antibodies accompanies a later illness. In other words, a positive heterophil test with consistently normal differential cell counts suggests that the illness being studied is not infectious mononucleosis. The patient with infectious mononucleosis, on the other hand, will have both hematologic and serologic evidence of the disease.

Discussion

It is difficult to understand the reluctance to accept a lymphocytosis and atypical lymphocytes as essential features of infectious mononucleosis. This lack of esteem is seen in case reports which fail to include a differential count, or where the count is normal or even shows a neutrophilia. Lack of enthusiasm for the atypical lymphocyte stems in part from the knowledge of their occurrence in many other diseases. The significant point is that in infectious mononucleosis they are sustained at levels not found in other diseases. Another factor contributing to the neglect of blood findings has been the failure to realize that heavy or poorly stained smears, especially those made after the febrile period, fail to demonstrate atypical lymphocytes clearly.

I have never seen a case of infectious mononucleosis unaccompanied by a typical smear. This does not imply that only cases showing a lymphocytosis have been tested for heterophil antibodies. For many years I have frequently checked for the presence of heterophil antibodies in many diseases simulating infectious mononucleosis.[2] Each year I see the results of hetero-

phil tests on many patients with borderline or normal differential counts, requested by physicians unfamiliar with the requisite blood picture in this disease. I have never seen a positive heterophil test with a normal differential count except in the rare instances where the patient was known to have had infectious mononucleosis earlier.

It is not known how these findings would be modified by associated conditions, because these patients were in robust health up to the time of their illness. In this connection, little or no change in the expected atypical lymphocyte response has occurred in patients with concurrent infectious mononucleosis and streptococcic pharyngitis.[18] On the other hand, some of the lesser shifts in the lymphocyte pattern were seen in patients with a concurrent Vincent's angina. Because of the young age group primarily afflicted by this disease, it does not seem likely that the question of a second disease masking expected changes in the lymphocyte pattern would often need to be considered.

Significant titers of heterophil antibodies have been reported in a wide variety of disease states. However, in the great majority, absorption with guinea pig kidney has removed all or almost all of the antibody. On the basis of incomplete absorption studies, positive heterophil tests in rare cases of leukemia and Hodgkin's disease have apparently been due to the presence of infectious mononucleosis-type antibodies. In other words, guinea pig antigen failed to remove much of the antibody. However, the failure to repeat the tests and too sketchy clinical and hematologic data have usually made critical evaluation impossible. In almost all cases, testing for presence of antibodies after beef cell absorption was neglected. Heterophil antibodies in the serum of individuals without infectious mononucleosis or serum sickness (so-called normal Forssman antibodies) are unaltered or partially removed after absorption with beef cell antigen, but completely removed in the two other conditions. These clear-cut findings, especially in cases with low presumptive titers and equivocal guinea pig results, make beef cell absorption a critical step in the differential diagnosis.

In the evaluation of a given case it should be remembered that a positive heterophil test may indicate:

1. Acute infectious mononucleosis. I should like to add here that, although I have been on the look-out for examples of recurrent or chronic infectious mononucleosis for many years, no evidence to support such a diagnosis has ever been found. The published accounts of such occurrences seen by the writer have been far from convincing.

2. Antibodies persisting from an earlier, possibly undiagnosed attack of infectious mononucleosis.

3. Nonspecific anamnestic reaction of heterophil antibodies.

In practice it is seldom necessary to do differential absorption tests. The prime indication is a positive presumptive test unaccompanied by typical hematologic findings. When it is found that the differential absorption

formula for infectious mononucleosis-type antibodies is positive with persistently normal differential counts it points to (2) or (3) above. Other indications for differential absorption tests are an incomplete clinical syndrome, such as the absence of posterior cervical adenopathy or fever, some atypical clinical sign, and persistently low titers, especially in the presence of severe systemic disease. In the presence of a diagnostic blood picture, differential absorption tests in the last three categories are reassuring rather than essential. Thus the more careful the study by simple clinical and hematologic methods, the less will the necessity to do differential absorption tests arise.

Summary

The wide range of blood pictures reported in infectious mononucleosis, particularly the failure to specify a minimal level of atypical lymphocytes, has long constituted a weak link in the evidence essential for the diagnosis. In the population studied, all patients had a minimum of 20% or 1,400 atypical lymphocytes near the time of the fever peak. Further analysis has shown that we can state with 99.9% confidence that at least 96.6% of all future patients with infectious mononucleosis will have differential counts of this order or higher. These findings suggest that the criterion of a few atypical lymphocytes should be revised upwards. All cases with total white counts of over 11,500 had 3,000 or more atypical lymphocytes; this level is pathognomonic for infectious mononucleosis.

While positive presumptive tests for heterophil antibodies have been reported in many disease states, there is no satisfactory evidence that a positive differential absorption test for infectious mononucleosis-type heterophil antibodies can be duplicated by any other condition. The need for differential absorption tests should be based more on atypical clinical and hematologic features of the illness than on titer levels alone.

It would appear that heterophil antibodies persisting from earlier, unrecognized attacks of infectious mononucleosis may sometimes explain the paradox of a positive heterophil test unaccompanied by characteristic clinical and hematologic features of this disease. There is also evidence that a resurgence of heterophil antibodies may, in rare instances, accompany some illnesses following infectious mononucleosis. These considerations emphasize the fallacy of basing the diagnosis on a positive heterophil test per se. While either a mononucleosis or a positive heterophil test gives assurance that the disease is infectious mononucleosis, each may occur independently in other situations. Not one or the other but both are essential to the diagnosis of infectious mononucleosis.

Summario in Interlingua

Le interpretation del datos hematologic in mononucleosis infectiose debe esser basate super le studio de frottis tenue, facite durante le periodo de febrilitate del morbo. A iste stadio, lymphocytos atypic de configurationes le plus floride es

presente. Plus tarde in le curso del morbo il deveni impossibile differentiar iste cellulas ab altere cellulas mononucleari con le mesme grado de certitude.

In 200 hospitalisatos studiate per diurne numerationes sanguinee, le lymphocytos atypic variava al tempore del febre maximal inter 20 e 67%. Le numeration absolute del lymphocytos atypic variava inter 1.400 e 13.500. Omne le numerationes total de 11.500 o plus includeva al minus 3.000 lymphocytos atypic. Numerationes de iste ordine, si illos persiste, es pathognomonic pro mononucleosis infectiose. In 370 casos, le numeration del neutrophilos al fin del periodo de febrilitate esseva infra 50% sin ulle exception. Novanta-sex pro cento de ille casos monstrava minus que 40% de neutrophilos. Iste constatationes suggere que le diagnose de mononucleose infectiose debe esser considerate como multo dubitose si normal numerationes differential persiste.

Positivitate del tests presumptive pro anticorpore heterophilic ha essite reportate in un grande varietate de morbos, sed il ha nulle base pro supponer que anticorpore heterophilic del typo incontrate in mononucleosis infectiose se disveloppa in ulle altere condition. Le technica a absorption in cellulas bovin (que es communmente omittite) debe esser includite in omne test de absorption differential.

Es presentate duo explicationes possibile pro le paradoxo que positivitate del tests heterophilic occurre con non-diagnostic numerationes differential. Elevationes significative de titros heterophilic—apparentemente representante non-specific reactiones anamnestic—esseva demonstrate in patientes con pneumonia atypic, non-differentiate infectiones respiratori, e pharyngitis streptococcic. Omne iste patientes habeva essite tractate per le autor pro mononucleosis infectiose a periodos de usque a un anno retro, e il esseva cognoscite que ante le nove maladia illes habeva habite basse titros de anticorpore. In plus, anticorpore que persiste depost un previe e non diagnosticate attacco de mononucleosis infectiose pote esser responsabile pro le positivitate del test heterophilic durante un subsequente maladia que es non relationate a mononucleosis infectiose. In iste situation le origine del anticorpore non esserea suspicite. Titros de 1:224 ha essite trovate in patientes asymptomatic cinque menses post un attacco ordinari de mononucleosis infectiose.

Iste considerationes sublinea le fallacia de voler basar le diagnose de mononucleosis infectiose exclusivemente super le positivitate de un test heterophilic. In patientes con mononucleosis infectiose on debe expectar un alte numeration de lymphocytos atypic a parte le positivitate del test heterophilic.

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THE SIGNIFICANCE OF THE LUPUS GLOBULIN–NUCLEOPROTEIN REACTION * †

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The description of the L.E. phenomenon by Hargraves is recognized as an important milestone in the advance of our knowledge of the rheumatic diseases.[1] This observation has aroused a great increase in interest in disseminated lupus erythematosus. In particular, the L.E. phenomenon has attracted the attention of investigators because of the feeling that knowledge of its mechanisms would reveal other important clues regarding the disease. Presented here is a review of some recent investigations related to this problem.

Interaction of Lupus Globulin and Nuclei

Particularly pertinent to our discussion is the work of Haserick,[2] who demonstrated that the L.E. factor is a component of the gamma globulin fraction of the serum proteins. More recently Miescher [3] reported that when serum from patients with lupus was incubated with a suspension of cell nuclei the ability to induce L.E. cells was eliminated. This observation indicated that the lupus factor was either destroyed by exposure to nuclei or removed from serum by combination with them. It has been possible to demonstrate by use of an immunochemical technic that under these conditions a globulin factor from serum does combine with nuclei.[4, 5] Certain other findings of interest have developed as a consequence of this observation.

The method used in the early part of these studies was the fluorescent antibody technic of Coons.[6] This method uses a fluorescent dye chemically bound to antiserum as a tracer or sensitive specific stain of an antigenic substance in sections of tissue. The application of the method to the study of this problem is illustrated in figure 1. When serum from a patient with lupus is placed on a section of tissue a globulin factor is bound firmly to the nuclei. After other serum proteins are removed by washing, fluorescent antihuman globulin will then react with this bound globulin, causing bright green fluorescence of nuclei when the section is examined under the microscope with ultraviolet light. With other serums there is no reaction of

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globulin with nuclei, and therefore no localization on nuclei of the fluorescent antibody. Results such as these have indicated that there is a globulin with a marked affinity for nuclei in serum from patients with disseminated lupus. This observation has been amply confirmed by others using this technic.[7, 8] Similar results were also obtained with cytochemical methods.[9] In the studies reported by the latter group of workers it was found that the change in staining which occurs when nuclei are exposed to lupus serum is due to accumulation in the nucleus of appreciable amounts of additional protein, rather than depolymerization of DNA to which this had previously been attributed.[10]

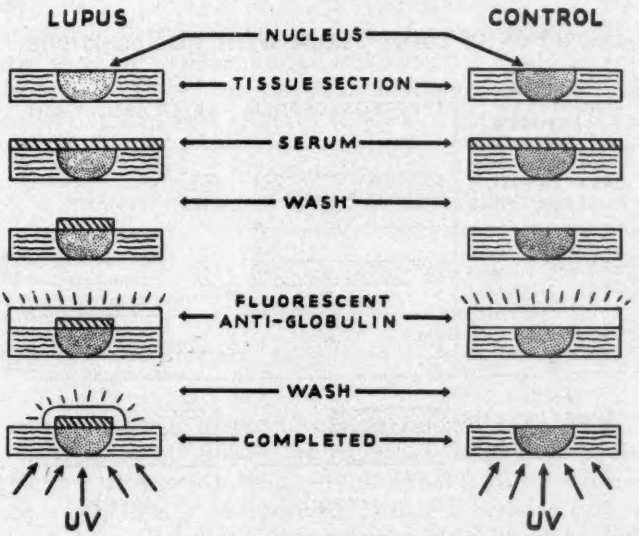

FIG. 1. Reaction with nuclei of globulin factor from serum of patients with disseminated lupus as demonstrated with fluorescent antibody (antihuman globulin).

LUPUS GLOBULIN REACTION WITH NUCLEOPROTEIN: THE FLUORESCENT SPOT TEST

Studies were carried out with the object of identifying the nuclear factor in this reaction. As a result of experiments involving the effects of enzymes and of various extraction procedures, it has been established that the active component of the nucleus is in the desoxyribonucleoprotein fraction. Drops of calf thymus nucleoprotein dried on slides can be tested for the binding of lupus globulin in the same way as was done with intact nuclei, and with such spots the activity of serum specimens can be titrated.[11, 12] In this test, dilutions of serum are placed on nucleoprotein spots. After 30 minutes, excess serum is washed away. When fluorescent antihuman globulin is placed on the spots it becomes bound if human globulin has previously re-

acted with the nucleoprotein. The highest dilution causing fluorescence of a spot under these conditions is the titer of that serum specimen. This technic was used to conduct a series of additional studies.

Lupus Globulin-Nucleoprotein Interaction and the L.E. Phenomenon

In one group of experiments, titration of serums was done before and after they were incubated with a suspension of nucleoprotein. Typical results of such an experiment are illustrated in figure 2. The affinity of the serum for nuclei and for nucleoprotein was reduced and its ability to induce

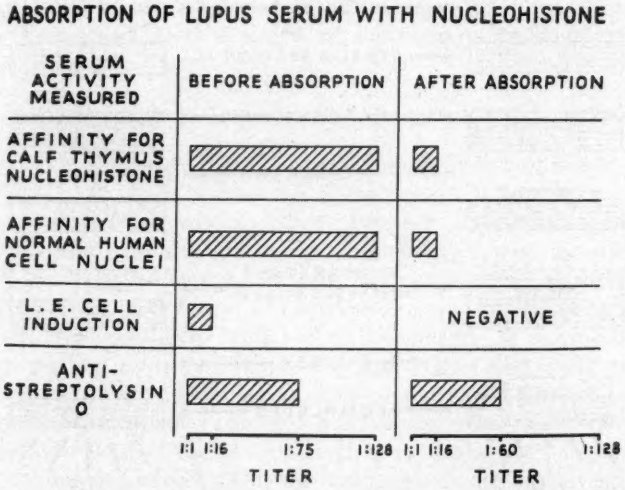

Fig. 2. Effect of absorption with nucleoprotein (nucleohistone) on titer of lupus globulin and induction of L.E. cells by serum from lupus erythematosus patients.

the L.E. phenomenon was eliminated by this procedure. The results of the antistreptolysin O test and measurement of individual serum protein fractions indicated that other components of the serum globulins were unaffected except to an extent consistent with slight dilution. These results may be interpreted as indicating that the interaction between this globulin factor and nucleoprotein is an essential early step in the L.E. phenomenon.[12]

Tests with nucleoprotein spots were done with 369 human serums.[13] Results of these tests are summarized in table 1. The test was positive in all of 35 patients with disseminated lupus, often in high titer. Three of these patients had never exhibited a positive L.E. test. Of these 35 serums from patients with lupus, 34 were tested in a standard procedure for demonstration of the L.E. phenomenon. Fourteen of the 34 were positive, a proportion of positive tests consistent with the results of others when single

tests have been done in a group of cases.[14] With these serums, all of which contained the globulin factor, there was no greater frequency of positive L.E. tests with higher titer of the factor. This raised the question of possible involvement of other variables. The exact conditions affecting phagocytosis are undoubtedly multiple and certainly not completely known. Recently, Finch and Detre have described inhibition of phagocytosis by serum of most patients with disseminated lupus.[15] This observation provides one possible explanation for the lack of correlation between occurrence of positive L.E. tests and titer of lupus factor. Their observation may explain the frequent occurrence of negative L.E. tests in patients known to have disseminated lupus.[14]

Our present understanding of the L.E. phenomenon may therefore be summarized as follows: When normal leukocytes are incubated with serum from patients with disseminated lupus an antibody-like protein reacts with the nucleoprotein component of nuclei of some of the cells. This accretion

TABLE 1

Reactions of 369 Human Serums with Nucleoprotein Spots

Diagnosis	No. Tested	No. Positive
Disseminated lupus	35	35
Rheumatoid arthritis	42	4
Biologic false-positive serology	17	4
Scleroderma	3	1
Dermatomyositis	2	1
Hypersensitive drug reaction	16	1
Miscellaneous diseases	254	3

of protein causes a change in staining characteristics of the nucleus. Leukocytes are attracted to this globulin-coated material and phagocytosis occurs, resulting in formation of L.E. cells. With serum from some patients with lupus there is inhibition of phagocytosis, causing a negative L.E. test even though the globulin factor is present. In the initial phase of the reaction only some of the nuclei become coated with the globulin factor. It is believed that these are nuclei of cells damaged physically due to manipulation. There is no published information indicating that there is any direct action of serum or plasma from lupus patients on leukocytes which makes available the nuclear material for participation in the reaction.

Detection of Lupus Globulin with Labeled Antiglobulin as a Diagnostic Aid

Other serums on which lupus globulin factor titration was done are indicated in table 1. In addition to the diagnostic groups listed, a large number of tests was done on serums from patients whose disease was not considered to be akin to lupus, but who presented various clinical or laboratory features commonly found in this disease. As mentioned above, lupus globulin factor was present in serums from all patients with lupus. There

were also positive tests at low titer in occasional individuals with rheumatoid arthritis, chronic biologic false-positive serologic tests for syphilis, dermatomyositis and scleroderma, and in patients with severe hypersensitivity reactions to drugs. Results with serum from patients with unrelated diseases were almost always negative, with the three exceptions indicated. Two of these were patients diagnosed as having syphilis. Review of the records of these two patients indicated that both probably are examples of chronic biologic false-positive serologic tests for syphilis.

It will be useful to consider briefly the methods used here for detecting the lupus globulin factor. Figure 3 illustrates schematically the important features of each of these procedures. In each the first important step is a reaction between lupus factor and nuclei or nucleoprotein. The difference

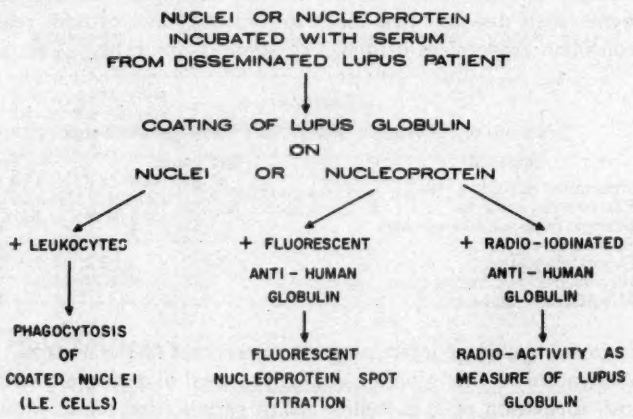

FIG. 3. Schematic representation of methods for detecting lupus globulin-nucleoprotein interaction.

in the procedures is in the indicator system utilized to detect this reaction. In the L.E. test, phagocytosis is the indicator used. This is simplest in performance but, because of the use of a delicate viable indicator system, is most likely to be affected by environmental conditions, or by factors such as that described by Finch and Detre.[15] Furthermore, satisfactory means of measuring the factor by this method have not been developed.

With the other two procedures, represented in figure 3, the presence of human globulin bound to nucleoprotein is detected with labeled antihuman globulin. The use of fluorescent antibody has already been discussed. Recent technical developments have reduced some of the difficulties in working with this method,[16] and the fluorescent spot test described above should be usable for detection of lupus factor in laboratories with very simple facilities. Investigation of other methods revealed that antihuman globulin labeled with I^{131} can also serve as a satisfactory test system.[17] Under

certain conditions which represent some modification of the procedure first described, the amount of radioactivity bound to a glass surface coated with nucleoprotein is in proportion to the amount of lupus factor in the serum being tested. Accumulated experience with this procedure is indicated in figure 4. Results are expressed as units which relate all serums tested to a single standard serum run with each group of tests. This method is more sensitive than the fluorescent antibody method in detecting small amounts of lupus factor, but results are otherwise quite comparable. In general, the

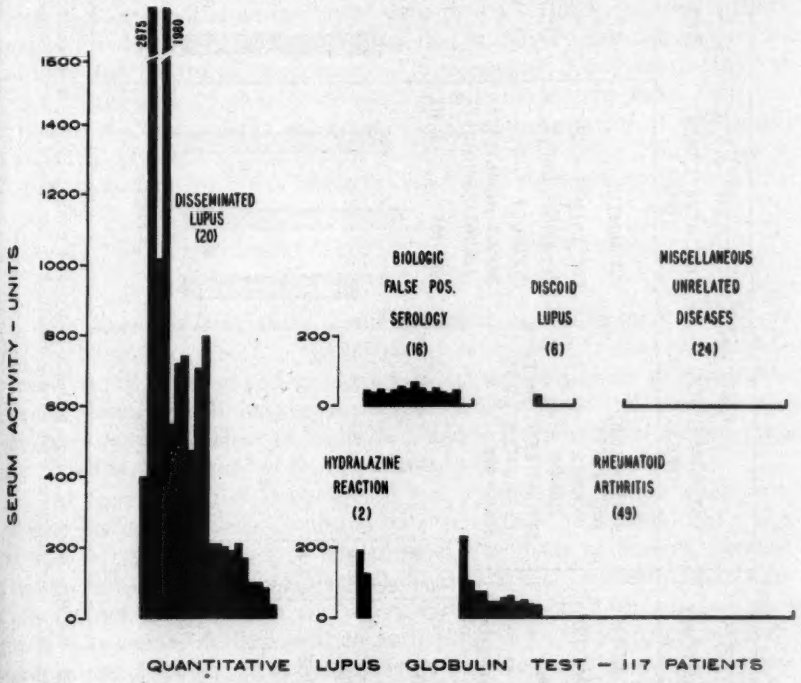

FIG. 4. Measurement of lupus globulin in 117 human serums using iodine^{131} labeled antihuman globulin.

factor is present in relatively large amounts in serum of patients with disseminated lupus, in smaller amounts in serum from some patients with the related syndromes indicated, as well as scleroderma and dermatomyositis, and from some patients with severe hypersensitivity reactions. These findings provide some indication of a possible biologic basis for the impression that there is a relationship between these diseases, and also for the occasional reports of positive L.E. tests in such patients.

The one patient with lupus with a particularly low level of activity had earlier had typical acute disseminated lupus, but at the time of this test had

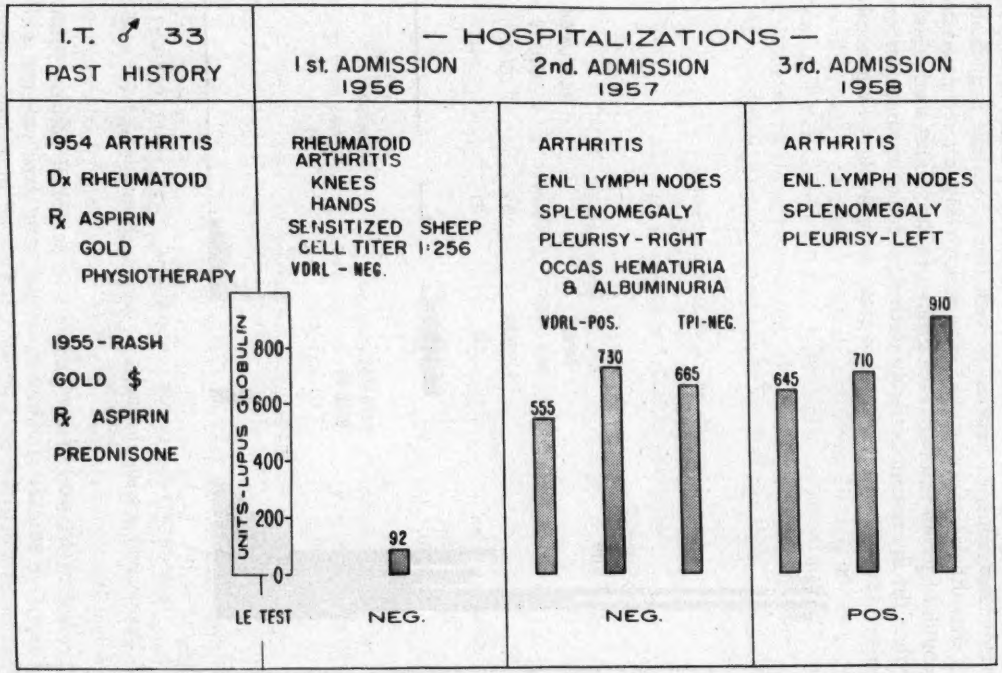

FIG. 5. Relation between levels of lupus globulin factor and clinical course in a patient who developed disseminated lupus erythematosus after having initially been considered to have rheumatoid arthritis.

no clinical or laboratory evidence of active disease. Experience with repeated tests on single individuals indicated that lupus factor levels vary in at least some individuals with changes in disease activity. One patient (figure 5) who was considered to have rheumatoid arthritis early in his disease, and who had a low level of lupus globulin factor at that time, subsequently developed a marked increase in level and developed findings consistent with disseminated lupus. Only during this patient's most recent admission has the L.E. test been positive, although tests for lupus globulin factor using labeled antiglobulin had been positive two years earlier. The finding of slight activity in serum of some patients with rheumatoid arthritis, and results in this individual, suggest that it may be possible to detect in advance the hazard of appearance of disseminated lupus in certain individuals. The use of phagocytosis as the indicator system places some limitation on the usefulness of detection of lupus globulin factor as a diagnostic aid. The data indicate that means of detection of this factor other than the L.E. test, such as the use of labeled antiglobulin, may remove this limitation.

Lupus Globulin-Nucleoprotein Reaction in Relation to Pathogenesis of Lupus

For several reasons there is much interest in this factor in relation to the auto-immune theory of pathogenesis of lupus. It has been demonstrable in the serum of patients with lupus more consistently than any other specific factor which has been studied. Furthermore, its characteristics are consistent with those of antibodies, and it is known that altered nuclei are found in the tissues of lupus patients.

The recent report of Robbins et al.[18] of complement fixation when serum of patients with lupus is incubated with cell nuclei adds additional weight to such a concept. No final statement can be made at present, however. Our knowledge of antibodies, and of other reactions between protein molecules, is not sufficient that the above findings can be taken as conclusive proof that we are dealing with an antibody-antigen reaction, although this appears rather likely. It is quite possible that auto-antibodies might appear as a consequence of alterations of tissue during a chronic disease, rather than as a cause of such changes. Further evidence is needed on the nature of the reaction and the mechanism whereby tissue injury characteristic of the disease might be produced. Recent reports of complement fixation with tissue extracts,[19] and our previous knowledge of other abnormal immune mechanisms in lupus,[20] suggest that the situation is complex and that multiple factors may be implicated. Hemolytic anemia due to an antibody-like circulating factor occurs in some individuals with lupus and not in others. For this reason it does not seem unreasonable to suggest that the presence or absence of other specific immune factors may account for other variations in disease manifestations from one patient to another.

Summary

Studies with the fluorescent antibody technic have shown that serums from patients with disseminated lupus erythematosus contain a globulin factor with a marked affinity for nuclei. With the use of this method, the nuclear component involved in the reaction was found to be in the nucleoprotein fraction of the cell nucleus. Evidence was presented indicating that this reaction is an essential step in the L.E. phenomenon. A clinical survey was made in which the affinity of human serums for spots of nucleoprotein was tested using fluorescent antiglobulin. Results indicated that the factor was consistently demonstrable in serum from lupus patients, and in low titer in serum from occasional patients with rheumatoid arthritis and other related diseases. Results of tests in which the factor was detected with antiglobulin labeled with iodine-131 indicated that this method might be used to measure the factor in human serums. The significance of these observations was discussed.

Summario in Interlingua

Studios per medio del technica a fluorescentia de anticorpore ha monstrate que seros ab patientes con disseminate lupus erythematose contine un factor globulinic que se distingue per su marcate affinitate pro nucleos cellular. In le presente reporto, le association del factor con nucleos es demonstrate, e certe characteristicas del factor es describite. Esseva monstrate que le factor seral reage con le fraction nucleoproteinic del nucleo cellular. Le elimination del factor ab le sero in consequentia de su absorption in nucleoproteina supprimeva le capacitate del sero de inducer le phenomeno del cellulas "L.E." Le reaction del factor in question con nucleos es un del prime phases in le phenomeno del cellulas "L.E."

Duo methodos esseva disveloppate pro le detection del factor per medio de marcate globulina anti-human. Le un utilisa antiglobulina fluorescente, e le altere utilisa antiglobulina marcate con iodo radioactive. Le technica a antiglobulina fluorescente es specialmente apte al uso in laboratorios con simple equipamento. Experientias con le duo technicas indica lor valor in le diagnose de lupus disseminate. Le resultatos pare significar que le mesuration del concentration de iste factor pote esser de valor in le evalutation del activitate del morbo e possibilemente in prognosticar le risco del apparition de lupus disseminate in certe individuous. Le signification possibile del factor in le pathogenese del morbo es discutite.

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SHOCK AND ACUTE ABDOMINAL SYMPTOMS COMPLICATING ACUTE IDIOPATHIC PERICARDITIS *

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Since Barnes and Burchell [1] showed the value of electrocardiographic interpretation in differentiating acute idiopathic pericarditis from acute coronary occlusion, there have been numerous reviews and case reports of the various manifestations of acute idiopathic pericarditis. Shock, with or without tamponade, has been rarely associated with idiopathic pericarditis. The presence of signs of acute abdominal disease at the onset of acute pericarditis, although infrequent, has been recently emphasized.[2]

Carmichael and co-workers, reviewing 50 cases with respect to clinical, laboratory and follow-up data,[3] commented on the infrequent occurrence of signs of circulatory collapse in acute pericarditis. In several reports of large series of patients, signs of circulatory collapse were not noted.[4, 5, 6] Only one of the 23 cases of acute idiopathic pericarditis reviewed by Reid et al.[7] developed an imperceptible blood pressure secondary to cardiac tamponade.

In 1944 Wolff reported five cases of acute pericarditis simulating acute myocardial infarction.[8] One of these, a 41 year old male, was observed to have a fall in blood pressure to shock level three days after the onset of chest pain without evidence of tamponade. Barnes and Burchell [1] recorded the history of a 34 year old male who was observed to be in shock after two hours of severe chest pain. In the absence of cardiac tamponade, shock was considered to be secondary to acute coronary insufficiency or myocardial infarction. Acute pericarditis was not suspected until an electrocardiogram disclosed changes characteristic of acute subepicardial myocarditis.

Acute abdominal symptoms at the onset of acute idiopathic pericarditis, while not rare, are infrequent enough to escape consideration in a preoperative differential diagnosis. The result may be an unnecessary abdominal exploration.

Abdominal pain as the initial or major symptom was noted in the early descriptive literature of the clinical manifestations of acute pericarditis.[9] However, until the last few years, case reviews have dealt little with this aspect of the syndrome.

Of the 50 cases reviewed by Carmichael et al.[3] one had pain limited to the

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abdomen and three had radiation of pain to the epigastrium. Powers, Read and Porter [2] noted that five of 13 patients with acute idiopathic pericarditis had significant complaints of abdominal pain. Reid and co-workers [7] recorded that six of 23 patients had epigastric pain, with nausea and vomiting occurring in five of these and occasionally preceding manifestations of pericarditis. After the onset of abdominal symptoms, chest pain invariably was noted to be present within 72 hours, often accompanied by friction rub.

The following cases are presented for the purpose of directing attention to the presence of shock and acute abdominal symptoms complicating the onset of acute idiopathic pericarditis.

Case Reports

Case 1. A 29 year old white male mechanic entered the hospital because of upper abdominal pain and vomiting for 36 hours prior to admission. Fever of 102° F. and profuse sweating were concomitant with pain. Two days before admission he had had a runny nose, a nonproductive cough and malaise. The next day nausea and an aching epigastric pain progressed steadily in intensity and were followed by vomiting. Localized epigastric pain was intensified by lying down, especially on the left side, and by deep inspiration. Pain was relieved by upright posture. There was no significant history of previous illness or contact with tuberculosis.

On admission the patient was in acute distress from severe epigastric pain. He was supporting his upper abdomen with his hands and occasionally retching. Blood pressure was 74/50 mm. of Hg; pulse, 120/min.; respiration, 24/min.; temperature, 100° F. His lungs were clear. The heart was not enlarged to percussion, the heart sounds were of fair quality, cardiac rhythm was regular, and no gallop, murmurs or rubs were heard. The abdomen was flat and symmetric, with marked tenderness in the epigastrium and right upper quadrant. There was guarding of the right rectus muscles, with rebound tenderness. Bowel sounds were present. The liver and spleen were not felt. There was no tenderness on rectal examination, and the stool specimen was negative for occult blood.

The white cell count on admission was 15,400 per cubic millimeter, with 73 neutrophils, 17 lymphocytes, 8 monocytes and 2 eosinophils. Hemoglobin was 15.6 gm.%. Serum amylase was 74 units%. Admission chest film showed a normal cardiac silhouette and clear lung fields. The abdominal films revealed no evidence of free air. An electrocardiogram taken two hours after admission showed changes of acute pericarditis consisting of elevated S-T segments and upright T waves in Leads I, II, aVL, aVF and V2-6, and depressed S-T segments in Lead aVR.

Additional laboratory data included an antistreptolysin titer of 50 Todd units on two occasions: C-reactive protein was 1 plus. Serum Wassermann, clotted peripheral blood L. E. test, blood cultures and sputa examinations for *Mycobacterium tuberculosis* were negative.

An intravenous infusion of norepinephrine resulted in a prompt elevation of blood pressure to normal levels. During the next 18 hours the patient progressively developed neck vein distention, a rapid, weak, paradoxic pulse, moist basilar pulmonary râles, and an enlarged and tender liver. A second chest film at this time showed no significant change in heart size. Approximately 24 hours after admission, pericardial aspiration removed 200 c.c. of cloudy yellowish fluid. This was followed by marked clinical improvement and a reduction of the area of cardiac dullness. Cultures of the pericardial fluid for the usual aerobic organisms and *M. tuberculosis* were negative; a stained smear showed an occasional white blood cell, but no bacteria were seen.

Norepinephrine was required to maintain an adequate blood pressure during the first five days of hospitalization. On the fourth hospital day the temporary discontinuance of norepinephrine was followed by a complaint of epigastric pain and a drop in blood pressure to 60/40 mm. of Hg. There was no evidence of recurrent cardiac tamponade. Blood pressure returned to normal when norepinephrine was resumed.

A systolic friction rub was heard only on the seventh hospital day. It was located to the left of the sternal border in the second intercostal space, and was present only in the supine position. There was no chest pain associated with the friction rub.

Serial electrocardiograms over the next 10 weeks showed the return of S-T segments to the base line, followed by T wave inversion in Leads I, II, aVL, aVF and V2-6.

The patient's course was punctuated by reçurrent, transient epigastric pain of less intensity than the initial episode. Recurrent pain was not associated with electrocardiographic changes, leukocytosis, elevation of the erythrocyte sedimentation rate or fever. Skin tests with P.P.D., coccidioidin and blastomycin were negative. There was a 2 plus reaction to histoplasmin 1–100.

Follow-up examinations three months later disclosed no clinical evidence of pericarditis, and the electrocardiograms were considered to be within normal limits.

Comment: The presenting findings initially suggested the presence of an acute surgical abdomen. Subsequent examinations disclosed no significant change in peristaltic bowel sounds or development of rebound tenderness. The basis of these findings was not clear until changes compatible with acute pericarditis were seen in an electrocardiogram.

It should be noted that shock preceded clinical signs of cardiac tamponade, and chest films were not helpful in demonstrating pericardial effusion. A rapid accumulation of pericardial fluid may produce cardiac tamponade with a small volume of effusion. The relatively inelastic properties of the pericardium would account for this, as well as the absence of change in the roentgen cardiac silhouette.

Chest pain was not present during the patient's course, even when a precordial friction rub was heard on the seventh hospital day. The need for norepinephrine for five days suggests an associated myocarditis of relatively severe degree. Recurrent epigastric pain concurrent with the drop in blood pressure may have been due to diminished coronary blood flow. It is of interest that the recurrent epigastric pain was similar to the pain on admission.

Case 2. A 29 year old white male hairdresser was admitted to the hospital complaining of chest pain and vomiting for 24 hours. Two days before admission he had had a mild headache, followed by chills and fever. The next day fever increased to 103° F., accompanied by a dry cough with mild chest discomfort. Several hours later an aching chest pain developed, accompanied by "numbness" of the chest and both shoulders. Pain radiated to the upper abdomen and interscapular area. The following day the patient began to vomit. The referring physician was unable to obtain a blood pressure, and sent the patient to the hospital with a diagnosis of perforated peptic ulcer and shock.

When he arrived at the hospital the patient's skin was a slate-gray color and he

was in acute distress from chest pain. Blood pressure and pulse were not obtainable. Temperature was 97° F. His neck veins were not distended. The pharynx and lungs were normal. The area of cardiac dullness was not enlarged; heart sounds were very faint, and no murmurs or rubs were heard. There was minimal epigastric tenderness, and bowel sounds were present. The extremities were cold and cyanotic.

The white cell count was 16,600 per cubic millimeter, with 95 neutrophils and 5 lymphocytes. Hemoglobin was 14.2 gm.%. The urine specific gravity was 1.023. The initial urinalysis showed a trace of protein, 2.5 gm.% sugar, 2 plus acetone, many hyaline and granular casts, and five to 10 white blood cells per high power field. Three subsequent urinalyses were normal, and a fasting blood sugar was 54 mg.%. Serum glutamic oxalo-acetic transaminase was 136 units (upper limit of normal, 40 units). Subsequent serum transaminase determinations two and three days after admission were 91 units and 39 units, respectively. Antistreptolysin titer was 25 Todd units. Admission electrocardiogram had S-T segment elevation in Leads I, II, III, aVF and V3-6, and S-T depression in aVR and V1. The P-R interval was 0.12 second. A chest film taken the second hospital day did not show cardiac enlargement. Heterophil, cold agglutinins, clotted peripheral blood L. E. test, serologic test for syphilis and blood culture were negative. The blood urea nitrogen was 14 mg.%.

Shortly after admission the patient was given an infusion of norepinephrine, which resulted in a prompt return of blood pressure to normal levels and was accompanied by an improvement in the quality of heart sounds. The next day norepinephrine was discontinued. Except for a mild nonproductive cough he improved rapidly and his course was uneventful. During convalescence there was no evidence of pericardial effusion, and no pericardial or pleural friction rubs were heard. Serial electrocardiograms showed the return of elevated S-T segments to the isoelectric line, followed by T wave inversion in Leads I, II, III, aVF and V3-6, and T wave elevation in Lead aVR.

Seven months after hospitalization, physical examination and an electrocardiogram were normal.

Comment: The combination of shock and elevated serum transaminase associated with acute idiopathic pericarditis was an unusual finding. There were several features of the patient's illness which, viewed together, suggested the presence of acute pericarditis rather than acute myocardial infarction. The patient was young, he had no previous history of angina or hypertension, and diabetes was not evident during hospitalization. He had had an upper respiratory infection just prior to the onset of chest pain. The electrocardiogram disclosed changes characteristic of the acute subepicardial myocardial injury that is associated with pericarditis.

Case 3. A 44 year old Negro office machinery repair man was admitted to the hospital with abdominal pain of 10 hours' duration. His illness had begun on the evening prior to admission, when he had noted that his "stomach" felt "numb, like there was no circulation." Several hours later he was awakened by severe epigastric and low substernal pain. A milder pain was also present in the left shoulder. Abdominal and substernal pains were aggravated by inspiration and supine position, and reduced by leaning forward or standing upright. He was seen by a physician, who noted extreme abdominal tenderness accompanied by muscle rigidity and definite rebound pain, and referred the patient to the hospital with a diagnosis of a perforated peptic ulcer.

There was no history suggestive of recent upper respiratory infection, rheumatic fever or tuberculosis.

Upon admission the patient was in acute distress from abdominal pain. His blood pressure was 130/90 mm. of Hg; pulse, 104/min.; respiration, 24/min.; temperature 100° F. The pharynx and lungs were normal. The area of cardiac dullness was not enlarged, and the heart sounds were of good quality. There was a harsh precordial systolic pericardial friction rub; no murmurs or gallop was present. There were marked guarding and tenderness of the upper abdomen; however, rebound tenderness was not elicited. Bowel sounds were hypoactive. The liver and spleen were not enlarged. No tenderness was noted on rectal examination.

The admission white count was 14,600 per cubic millimeter, with 95% neutrophils. Hemoglobin was 13.4 gm.%. Erythrocyte sedimentation rate was 18 mm. per hour. The urine was normal. Serum amylase was 92 units per 100 ml. Serum glutamic oxalo-acetic transaminase levels determined during the first 72 hours of hospitalization were normal. The initial electrocardiogram had elevated S-T segments in Leads I, II, aVL and V1-6, and inverted T waves in Lead III. A normal cardiac silhouette with platelike atelectasis at the right base was noted on chest x-ray. The abdominal film was negative for free air or calcific densities. The antistreptolysin titer was 125 Todd units, and C-reactive protein was 3 plus. Three clotted peripheral blood L. E. tests were negative. A heavy growth of alpha streptococci was cultured from the throat.

The patient was treated symptomatically without antibiotics. A few hours after the initial physical examination the pericardial friction rub disappeared, and in its place a soft apical systolic murmur was heard. Evidence of cardiac tamponade was not demonstrable. After 24 hours of hospitalization the patient was free of abdominal pain. On the third hospital day he was afebrile, and the second electrocardiogram showed T wave inversion in Leads II, III, aVF and V4-6. On the seventh hospital day there was a sudden onset of substernal and left chest pain. At that time a loud pericardial friction rub was heard over the fifth and sixth intercostal spaces along the left sternal border. Several hours later the rub had disappeared. The remainder of his course was uncomplicated.

Comment: The relationship of posture and inspiration to the patient's epigastric pain and the transient pericardial friction rub caused the admitting physician to suspect acute pericarditis. The diagnosis was confirmed by the electrocardiogram.

Discussion

It has been suggested that, due to our present state of ignorance regarding etiology, acute idiopathic pericarditis should be considered to be a syndrome rather than a distinct etiologic entity.[10]

Greater variations of this syndrome have become apparent subsequent to the increasing awareness of acute pericarditis.

Two of the three cases presented had severe abdominal pain within the first 36 hours of overt symptoms. Two of the patients presented findings of shock; concomitantly, one patient had chest and abdominal pain, the other had severe abdominal pain. Norepinephrine infusions were effective in the management of shock. All of the cases exhibited electrocardiographic changes compatible with acute pericarditis, as well as fever, leukocytosis and elevated erythrocyte sedimentation rate. Pericardial friction rubs, which

were limited to a few hours in duration and were of faint intensity, were heard in two of the patients. Serum glutamic oxalo-acetic transaminase was measured in two cases, and in one it was found to be elevated significantly during the first 48 hours of illness.

In most cases of acute pericarditis there will be findings which will suggest the diagnosis when the patient is first seen. Early in the course the patient may find some relief from pain if he leans forward from the waist. Because of this he will be reluctant to assume a supine position for examination. Acute pericarditis, acute myocardial infarction, pulmonary embolus and dissecting aortic aneurysm may all present with chest pain, fever, leukocytosis, elevated erythrocyte sedimentation rate, and an abnormal electrocardiogram.[11] The presence of pericardial and pleural rubs suggests pericarditis, whereas pericardial involvement due to pulmonary embolism or pleural involvement due to myocardial infarction is unusual. Dissecting aneurysm may be associated with a left hemothorax, with or without hemorrhagic effusion into the pericardium. In either case, the effusions are large and may follow pain by days or weeks. In patients with acute pericarditis in whom abdominal pain is severe, it may be noted that the bowel sounds are more active than would be expected in patients with acute abdominal inflammation,[2] even though the location and degree of pain with fever, leukocytosis and increase in erythrocyte sedimentation rate may suggest serious abdominal disease.

Peripheral vascular collapse and shock in two of the cases described here were probably due to severe subepicardial myocardial injury. This was suggested by the elevated serum glutamic oxalo-acetic transaminase in one case, and the necessity for norepinephrine infusion to combat shock in both cases. Shock did not respond to relief of pain.

Histologic studies have shown that the inflammatory reaction of acute pericarditis may involve the adjacent subepicardial myocardium.[12] Agress, Glassner and Binder [13] produced pericarditis in dogs and noted that the more severe instances of subepicardial myocarditis were associated with severe pericarditis. However, severe pericarditis was not always accompanied by a severe degree of myocardial change. Usually the electrocardiographic changes characteristic of pericarditis were found to be proportional to myocardial inflammatory changes. Less frequently there were severe inflammatory changes with minimal electrocardiographic changes.

Significant elevations of serum transaminase levels have been recorded in experimental pericarditis in dogs.[13] Transaminase elevations in these experiments were associated with moderate to severe subepicardial myocardial damage. Serum transaminase was not elevated, even with severe pericarditis, unless there was distinct myocardial injury. Nydick et al.[14] were also able to demonstrate significant serum transaminase elevations following experimental pericarditis in dogs. Such elevations were associated with extensive subepicardial myocardial necrosis. The presence of

myocardial necrosis was necessary before elevated serum transaminase levels were detected.

The majority of patients with idiopathic pericarditis have not been found to have elevated serum transaminase. Chinsky and associates [15] found normal serum transaminase levels in five patients with benign idiopathic pericarditis. Gelfand and Goodkin [16] commented that serum transaminase was normal in pericarditis. Two of the 11 patients with pericarditis reported by Nydick et al.[14] had elevated serum glutamic oxalo-acetic transaminase. One had advanced myelocytic leukemia, and the other had concurrent abnormal liver function tests. Included in their report were three patients with idiopathic pericarditis, each of whom had normal serum glutamic oxalo-acetic transaminase activity. Recently, Kalmansohn and Kalmansohn have reported two fairly typical cases of pericarditis with serum transaminase elevations.[17]

The pain of pericarditis is usually located in the precordial and substernal areas. Pain may be referred to the left side of the neck and shoulder by way of the phrenic nerve when the diaphragmatic portion of the parietal pericardium is irritated, or to the abdomen by way of the lower intercostal nerves when the more lateral portion of the diaphragmatic pleura is irritated.[18, 19] When pain is localized to the abdomen and is severe, the diagnosis may be difficult.

Powers and co-workers [2] noted the relative frequency of abdominal pain associated with acute idiopathic pericarditis. Thirteen cases were reviewed, emphasizing a location of pain and associated symptoms that suggested gastrointestinal rather than cardiovascular disease. Five of the cases had significant abdominal pain, four localized to the epigastrium, one involving the entire abdomen. Pain eventually migrated to the chest in all cases. Two patients had severe localized abdominal pain which suggested a probable perforated peptic ulcer and ruptured appendix. One patient was explored surgically and no evidence of abdominal disease was noted. These cases emphasize the quality and severity of abdominal pain that may be associated with acute pericarditis.

In acute pericarditis with abdominal pain the physical findings may be almost indistinguishable from the findings in acute peritoneal inflammation. During the first few days, abdominal pain with nausea and vomiting may be the primary symptom.[2, 7] Moderate to severe pain is often accompanied by nausea, vomiting, abdominal distention, tenderness and spasm. However, abdominal findings may not include rebound tenderness or absence of peristaltic bowel sounds. Exceptions will be noted, as in the third case described above, where early, transient rebound tenderness was elicited.

Acute idiopathic pericarditis often occurs in the 20- to 40-year age group. Consequently, cardiovascular disease may seem unlikely or unnecessary to rule out before surgery when acute abdominal pain is the primary and major symptom. An electrocardiogram and frequent precordial auscul-

tation before surgery may demonstrate the true etiology of what at first sight appears to be an "acute surgical abdomen."

Summary

Three cases are presented to direct attention to shock and acute abdominal symptoms that were associated with acute idiopathic pericarditis.

One of the cases that presented in shock had an elevation of serum glutamic oxalo-acetic transaminase activity. This was an unusual finding, and it probably reflected a severe degree of pericardial inflammation with concomitant subepicardial myocardial injury. Blood pressure responded promptly following the administration of norepinephrine in both cases with shock.

Abdominal pain may be a major symptom of acute pericarditis. When pain is initially confined to the abdomen and is accompanied by tenderness with guarding, the possibility of acute pericarditis can be easily overlooked. An electrocardiogram and frequent precordial auscultation are the most reliable means of recognizing the true etiology of symptoms and findings which at first may appear to be due to acute abdominal disease.

Summario in Interlingua

Es presentate tres casos pro illustrar le occurrentia de choc e acute symptomas abdominal in association con pericarditis idiopathic acute.

Collapso de vasos peripheric e choc es rar complicationes de pericarditis idiopathic. Tamen, il es probabilemente non inusual que le symptomas primari e major del morbo es acute dolores abdominal accompaniate de nausea, vomito, e sensibilitate abdominal sub pression. In le casos presentate, un signo de utilitate differential esseva le presentia de sonos de active peristalse intestinal, proque iste activitate excedeva lo que pote esser expectate in patientes con acute inflammation abdominal.

Un del patientes, qui esseva in choc, monstrava un elevation del activitate de transaminase glutamic oxalo-acetic del sero e etiam alterationes in electrocardiogrammas serial typic de pericarditis acute. Le elevation del activitate de transaminase seral esseva un constatation inexpectate e reflecteva probabilemente un grado sever de inflammation pericardial con damnification concomitante del myocardio subepicardial.

In le duo casos de choc, le pression del sanguine esseva promptemente re-elevate per medio de un infusion de norepinephrina.

Viste que pericarditis idiopathic acute occurre frequentemente in subjectos del gruppo de etate de inter 20 e 40 annos, le presentia de un morbo cardiovascular es facilemente considerate como multo improbabile quando le symptomas primari e major es dolores abdominal. Il es facile negliger pericarditis in un diagnose differential pre-operatori, de maniera que un operation abdominal es effectuate ben que nulle tal es requirite.

Frequente auscultation precordial e un electrocardiogramma es frequentemente capace a clarificar symptomas e constatationes que initialmente pareva esser causate per un "acute abdomine chirurgic."

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PERIODIC DISEASE: A CLINICOPATHOLOGIC STUDY *

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Introduction

Periodic disease, periodic idiopathic abdominalgia or periodic peritonitis is a disease of unknown cause characterized by short attacks of pain in the abdomen or elsewhere and associated with fever and leukocytosis. Such attacks recur regularly or irregularly over many years. During such attacks an acute inflammatory process involves the visceral and parietal peritoneum.[1] It is rather odd that intestinal adhesions, and consequent intestinal obstruction, do not occur in these patients despite the constant repetition of the serosal inflammatory lesions.

A number of these patients develop a "nephropathy" [2] after a few years and may die with renal failure. The cause of this "nephropathy" is not yet known.

The nature and cause of this disease are still in the realm of speculation, and there are no reports of autopsied cases in the medical literature, even in the articles most frequently referred to.

The purpose of this article is:

1. To report, probably for the first time, on the findings in two autopsied cases of periodic idiopathic abdominalgia.
2. To review briefly the clinical and anatomic manifestations of this disease as observed by the staff of the Clinical and Pathology Departments of the American University of Beirut.
3. To attempt to explain the nondevelopment of intestinal adhesions in spite of the repeated inflammation of the serosa.
4. To report for the first time the nature of the "nephropathy" that develops in some of these cases.
5. To make a few suggestions that may have a bearing on the cause and nature of this disease in the light of the observations in 1, 2 and 4, and what is found in the literature.

The experience of the staff of the American University Hospital is presented in this paper according to its chronologic development.

The First Two Cases and First Autopsy

In October, 1934, two brothers were admitted to the American University Hospital of Beirut. Both were from Baghdad, in Iraq. One was nine years of age, the other was six. Both had identical hospital charts describing 12-to-24-hour bouts

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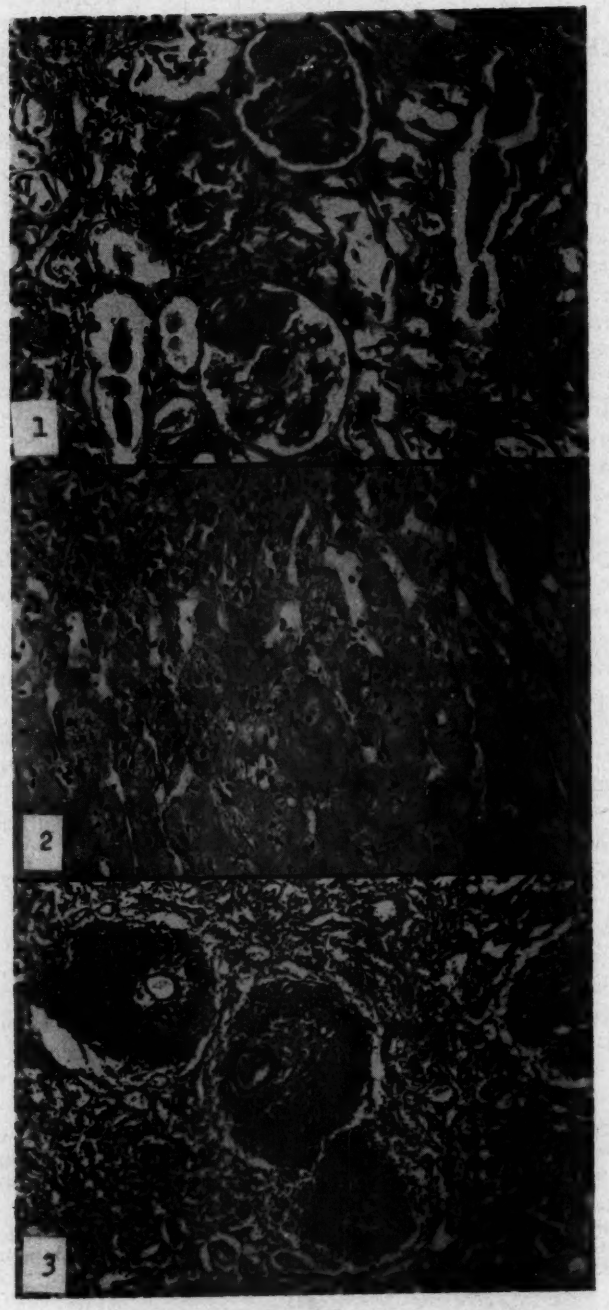


FIGS. 1–3.

of abdominal cramps, with fever sometimes reaching 40° C., recurring every seven days since the age of six months. Occasionally the fever came without pain, or the pain without fever. There were intervals as long as two weeks during which the boys were symptom-free.

Physical examinations were entirely negative except during an attack, when slight abdominal tenderness and epigastric hyperesthesia could be elicited.

The symptoms could not be attributed to any cause. Being from Iraq, they received intensive antimalarial and antiamebic treatment, but the course of their illness persisted unchanged.

During their short stay at the hospital no amebae or malarial parasites could be demonstrated. Kolmer's and Kahn tests were reactive.

The laboratory tests on the younger boy showed: hemoglobin, 70%; red blood cells, 5.2 million; white blood cells, 8,150; lymphocytes, 39%; monocytes, 5%; polymorphonuclears, 55%; basophiles, 1%. The urine was acid, with a specific gravity of 1.026, a faint trace of protein and an occasional white cell in the sediment. There were cysts of *Giardia lamblia* in the stools. An intravenous pyelogram was reported to show a decided difference between the right and left renal pelves at 12 and 25 minutes; the left was much larger and its shadow much denser. There were no opaque calculi. A cholecystogram showed no filling of the gall-bladder as the dye was eliminated by vomiting.

The older brother showed: hemoglobin, 68%; red blood cells, 3.96 million; white blood cells, 7,000; lymphocytes, 52%; monocytes, 5%; polymorphonuclears, 41%; basophiles, 2%. The urine was acid, with a specific gravity of 1:025 and an occasional white cell and a few hyaline casts in the sediment.

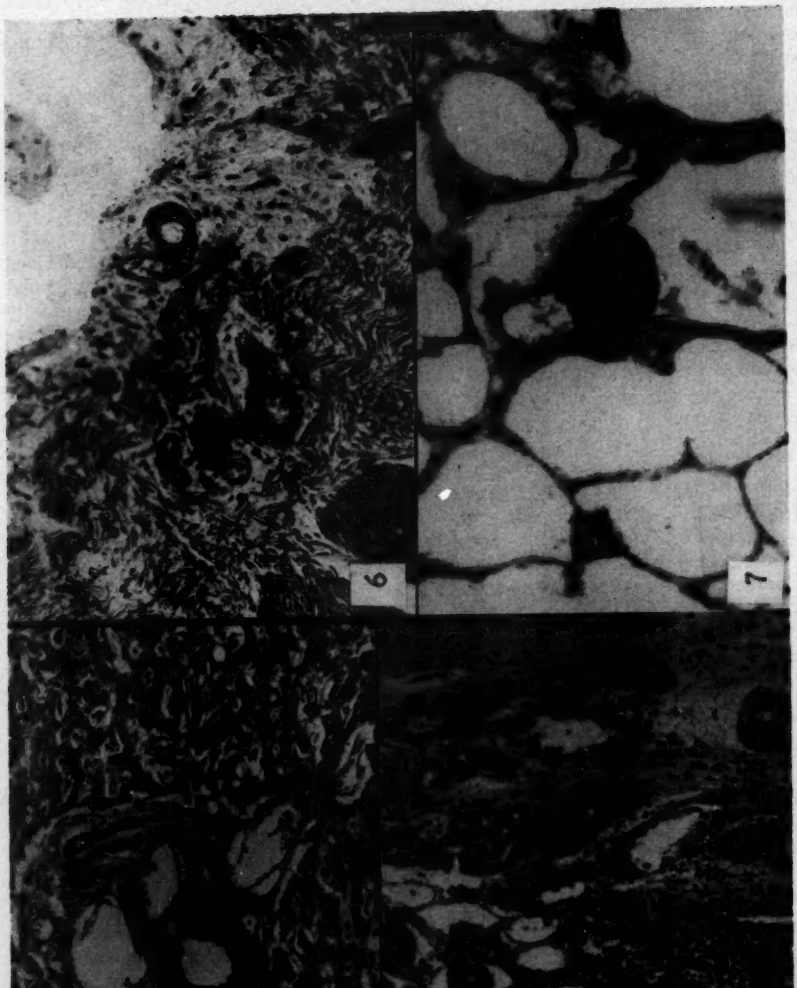
The older boy had one of these episodes during his stay in the hospital. Careful examination at the time was negative, and his blood culture was sterile. Agglutination tests for Malta fever were negative. The fever subsided the next morning.

At a later date an x-ray of the chest and a gastrointestinal series showed no abnormal findings. Four days later an intravenous pyelogram was reported to be negative, but during the procedure the appendix was found still to be filled with barium.

After the boys' discharge from the hospital the course of the disease remained unaltered, and when "periodic disease" became publicized their ailment was diagnosed as such. They were followed by some of the staff of the American University Hospital, who stated that their symptoms became more pronounced and the bouts continued with chronologic regularity. In the latter part of their illness they developed urinary trouble and uremia. The older brother died in Iraq; the younger died in Lebanon in 1941. His body was brought to the American University Hospital for embalmment. During the procedure the body was eviscerated.

Sections from these tissues showed severe amyloid deposition in the kidneys, adrenals and spleen that caused considerable diminution of the parenchyma of the organs (figures 1, 2 and 3). In the liver and pancreas the deposition did not extend beyond the vessels (figure 4). In the bowel the deposition was extensive in the vessels of the mucosa and serosa (figures 5 and 6). The two layers were edematous and showed loose infiltration by monocytes, lymphocytes, polymorphonuclear leukocytes, plasma cells, eosinophils and mast cells. There was ascites. The heart was free of amyloid. The lungs showed no parenchymatous lesions, but there were hyaline ball thrombi in many of the pulmonary vessels (figure 7). Some of the lymph nodes were involved.

FIG. 1. *First autopsy:* amyloid deposits in the glomeruli.
FIG. 2. Amyloid deposits in the adrenal cortex.
FIG. 3. Amyloid deposits in the white pulp of the spleen; in other sections the deposit involves the red pulp.



FIGS. 4–7.

EXPERIENCE AT THE HOSPITAL OF THE AMERICAN UNIVERSITY OF BEIRUT

During the last 24 years many cases of periodic disease have been diagnosed at this hospital. All had the typical history of bouts of pain and fever that came periodically. These patients were submitted to thorough studies in an attempt to explain their symptoms. Failure to find a satisfactory explanation or cause, and the ruling out of any condition with a clinical resemblance, led to our grouping these patients under the heading of "periodic disease."

Some of the cases were operated upon during attacks and had their appendices removed, and in some the peritoneum was biopsied. In some of these the histologic examination showed a mild acute serosal inflammatory reaction in the appendix or the parietal peritoneum or both. The reaction was nonspecific and appeared as edema, congestion and infiltration by polymorphonuclear leukocytes and round cells (figure 8).

I examined some of these specimens, keeping in mind the possibility of focal acute appendicitis. Serial sections of the appendices showed conclusively the absence of mucosal lesions.

In 1954 Reimann et al.[1] reviewed 72 cases of periodic disease that had been observed in hospital or clinics of the American University of Beirut during the preceding five years. They discussed the hereditary aspects of the disease and stressed some features of its morbid anatomy based on the study of the peritoneal biopsies and appendices removed during the attacks. The pathologic findings were restricted to inflammatory lesions similar to those described above.

After reviewing the slides of these and other cases, I was impressed by the following facts:

1. "Fibrils" of fibrin were very sparse in and on the serosa (figure 8).
2. Mast cells were present in the infiltrate.
3. The edema fluid seemed to contain a considerable amount of protein, as indicated by its strong affinity to eosin and its fibrinoid appearance in some sections (figure 9).

Further experience in this hospital showed that many of these patients developed urinary abnormalities during the attacks, in the form of moderate or severe albuminuria and some hyaline casts. Later in the course of their illness such urinary findings become constant. Indeed, some of these patients died with renal failure. This is in line with what Cattan et al.[2,3] in 1952 and 1955 described as a condition of "nephropathy" among their cases of periodic disease. The nature of the morbid anatomy in the kidneys remained obscure, since no autopsies were reported among their cases.

FIG. 4. *First autopsy:* amyloid deposits in the intrahepatic vessels of the liver. Note how the parenchyma is spared.

FIG. 5. Severe involvement of the vessels in the submucosa of the intestines. Note the inflammatory reaction.

FIG. 6. Amyloid deposits of the vessels in the serosa of the gastrointestinal tract.

FIG. 7. Hyaline thrombi in the pulmonary vessels.

The Second Autopsy

In September, 1956, I had an opportunity to study some of the tissues of a 13 year old boy who had suffered from periodic disease during the previous six years and died as a result of renal failure. A detailed review of the clinical history, including the chemical studies, is a necessary introduction to the postmortem findings.

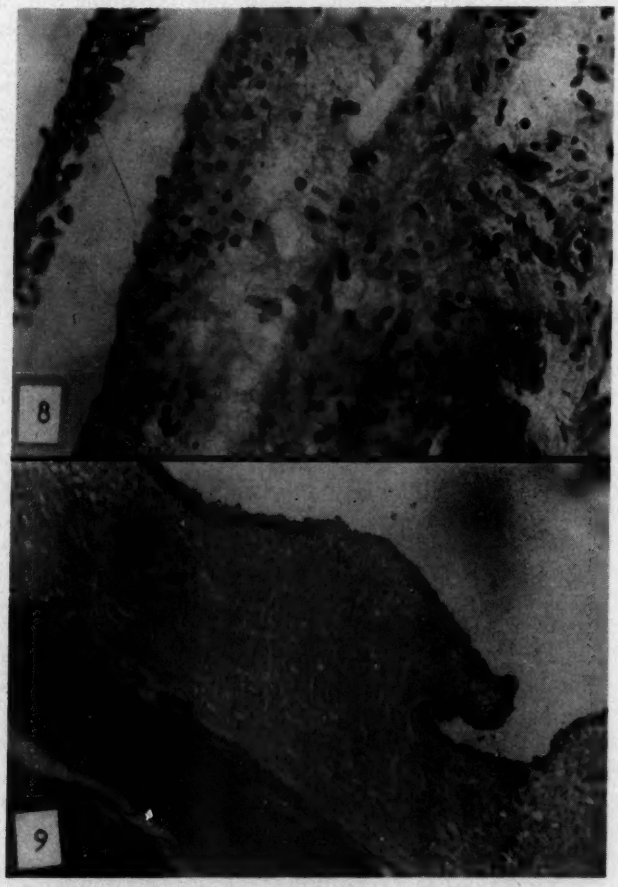


Fig. 8. *From surgical specimens:* inflammatory reaction in the serosa of the bowel. The infiltrate contains mast cells. Note sparsity of fibrin.

Fig. 9. The serosa of the appendix is edematous and the fluid takes eosin strongly, giving the serosa a fibrinoid appearance.

This boy's illness started at the age of eight years, in 1950, with repeated attacks of severe, diffuse pains in the abdomen, loin and chest which lasted from 18 to 24 hours and were accompanied by fever. In the beginning they occurred every month, then every two to three weeks, and finally every two to three days. In the absence of other findings the diagnosis of periodic disease was made. His paternal and

TABLE 1

Laboratory Data of Second Autopsied Case

Period	Total Protein gm.%	Albumin / Globulin	CO_2 c.p. mM/L.	Chlorides mEq/L.	Inorganic Phosphorus mg.%	Calcium mg.%	Potassium mEq/L.	Sodium mEq/L.	Hemoglobin gm.%	RBC Mill./mm.	Cholesterol mg.%	Creatinine mg.%	NPN mg.%	BUN mg.%	PSP	Urea Clearance	Urine Sp. Gr.
1954, March	2.4	1.2 / 1.2	20	95					11	3.2	382	0.5		8	55	67	1.006–1.017
April	3.1	1.1 / 2.0		106							467			8			
June	2.9	1.2 / 1.7		108					11	3.4	393			9			
October	2.7	0.8 / 1.9		103					9	2.5	264			15.9	50	21	1.006–1.010
1955, January	3.9	1.3 / 2.6		102	4.5	9.5			10	3.5	438		35	27	15	12	
July	4.8	2.4 / 2.4	5.7†	112	8.7	5.6			5.5	2.8	255			52	15	4.5	1.010–1.020
1956, June	6*		3.6†	105	6	4.6	2.2	136	5.6	2.1		12	75	53			
July	5.2		27‡	95†	8.6	3.3–5.7	4.2										
September	3.7	1.2 / 2.5	15	77	7.9	3.1	2.3	126	5.5	1.4		16	90	55–63			

* After transfusion.
† Could be corrected by alkali therapy.
‡ After correction of acidosis.

maternal grandmothers were first cousins. An older brother and one older sister suffered from periodic abdominalgia and stethalgia.

In January, 1954, this patient developed edema. From that time until his death his urine contained proteins and casts.

FIG. 10. *Second autopsy:* almost all glomeruli are involved in amyloidosis.
FIG. 11. The kidney medulla is relatively free of amyloid, but there is severe atrophy of its tubules.

His first admission to the hospital was in March, 1954. Physical examination showed a pale boy with generalized pitting edema. There were no abnormal findings in the abdominal organs. Temperature, 40° C.; blood pressure 80/45 mm. of Hg. White blood cell count was 26,000: unsegmented, 49%; segmented, 38%; lymphocytes, 9%; monocytes, 4%. Total proteins, 2.4 gm.%; albumin, 1.2; globulin, 1.2; chlorides, 95 mEq./L.; CO_2 combining power, 19.5 mM.; urea nitrogen, 8 mg.%; cholesterol, 382 mg.%. Electrophorogram showed the albumin to be 5.6%, globulin, 12.5% α_1, 49.5% α_2, 22.4% β, and 10% δ.

The child remained in hospital four months, during which time he had 16 attacks of abdominalgia and stethalgia at irregular intervals from three to 14 days, each lasting 24 hours and accompanied by fever, leukocytosis and neutrophilia with a shift to the left.

He received two courses of ACTH and was kept on a high caloric diet high in protein and low in fat. His edema varied somewhat in intensity but never disappeared completely. His blood pressure was always low. Urinary protein with Esbach's reagent oscillated between 1 and 7 gm./L. His total protein was never higher than 3.6 gm.%, with a globulin fraction always higher than that of the albumin. The serum cholesterol did not exceed 470 gm.%. His urinary findings did not change throughout his hospital stay (table 1). He was discharged in July with a definite increase in his edema and a 9 Kg. increase in his weight.

His second admission was in October, 1954, for edema and ascites. Three liters of fluid were removed from his abdomen and some chemical studies were performed (table 1).

He was discharged in December, 1954, to be re-admitted for the third time in January, 1955, for another check-up (table 1). At that time he had no edema.

He was readmitted for another month in July, 1955, complaining of weakness, drowsiness and loss of appetite during the previous two months. During this admission his anemia was corrected by transfusions. His low CO_2 combining power could be corrected to 21 mM by oral administration of calcium lactate and sodium citrate. However, the CO_2 combining power dropped back to 12 mM after discontinuation of such treatment. His hypocalcemia and hyperphosphatemia could not be corrected. The urea rose to 66 mg.%. The α_2 globulins remained high.

The patient's fifth admission was between May 31 and June 27, 1956, for anorexia, headache, carpopedal spasm and hypotonia. X-ray studies showed diffuse osteoporosis, but no signs of rickets or hyperparathyroidism. There were no calcifications in his kidneys. After the correction of his acidosis, tetany developed (table 1).

The last admission was in September, 1956, when he came in coma, with a pericardial friction rub, positive Chvostek's sign, and peroneal, radial and ulnar signs. He was having continuous convulsions and died on September 9, 1956 (table 1).

The findings at this autopsy were essentially similar to those described in the first autopsy: a severe amyloid infiltration of the renal glomeruli (figure 10), atrophy of its tubules (figure 11), and amyloid infiltration of the spleen as well as involvement of the vessels of the liver (figure 12). The loss of parenchyma in the kidney was severe, but there was almost no loss in the liver.

The early lesions in the renal glomeruli were reminiscent of wire-loops, and some of its vessels had an onion-peel appearance (figures 13 and 14). Had it not been for the histochemical identification of amyloid, these would have been reminiscent of the vascular and glomerular lesions of lupus erythematosus.

Discussion

During attacks of periodic disease an acute inflammatory process involves the serous surface of the cavity and some of its organs, thus producing the clinical symptom of pain in the region. The reaction is characterized by the presence of segmented neutrophils and round cells, among which a number of mast cells are encountered. The staining properties of the "edema fluid" indicate a high protein content. The formation of fibrin in the lesion is not striking. This sparsity of fibrin goes hand-in-hand with the presence of mast cells known to contain heparin. The absence of fibrin leaves no

FIGS. 12–14.

scaffold for any granulation tissue, and thus no chance for the development of adhesions and consequent intestinal obstruction.

Patients with periodic disease may develop urinary symptoms and may die as a result of renal failure. Our experience is in line with what Cattan and Mamou [2, 3] and others have described. The clinical observation on the first autopsied case and the detailed clinical study of the second indicate the existence of both progressive glomerular and tubular failures.

The kidneys in both autopsies showed severe amyloid infiltration involving the glomeruli and the smaller vessels; there was minimal amyloid deposit in the medulla, but considerable atrophy of the tubules, most likely on vascular basis. The histologic anatomy of these lesions is distinctive and different from that of glomerulonephritis: there is no decrease in the number of the glomeruli, no adhesions between the tufts and Bowman's capsules, and there is preservation of the glomerular pattern with few complete ball formations. The histochemical properties of this substance confirm its identification as "amyloid." Moreover, these two patients did not have hypertension, a well known clinical observation in renal amyloidosis.

It is therefore clear, at least in these two cases, that the cause of the "nephropathy" in periodic disease is renal amyloidosis.

Grayzel et al.[4, 5] reported experimental and clinical evidence that amyloid deposits may be reversible. If this is the case, it is safe to conclude that amyloidosis may be expected in patients with severe periodic disease who suffer from closely spaced, severe attacks which interfere with the complete resorption, during the remissions, of any deposited material in the relapse. This should throw light on the pathologic physiology of those cases that are relatively mild and do not die with renal failure. This concept of amyloid "deposition" and "resorption" should not seem strange if one keeps in mind that amyloid is a precipitated antigen-antibody complex. This point will be referred to again in connection with the relation of amyloidosis to collagen diseases.

The distribution of the amyloid in the two autopsied cases was rather unusual. It involved the vessels of the organs supplied by the celiac axis but without depleting the parenchyma of the epithelial organs. Special mention should be made of involvement of the vessels of the serous surface of the visceral peritoneum over the digestive tract. It is only in the kidneys and adrenals, not supplied by the axis, that there was severe diminution of the parenchyma. The distribution of the deposited amyloid is unlike the primary form, since the skeletal and cardiac muscles are spared. It is also unlike secondary amyloidosis, in which peritoneal and lymph node involvement is not an outspoken anatomic feature. Besides, there is absence of a

FIG. 12. *Second autopsy:* amyloidosis of the intrahepatic vessels. There is no deposit in the parenchyma, but it shows fatty infiltration and microscopic foci of focal necrosis.

FIGS. 13 and 14. Note the wire-loop appearance of the glomeruli and the lamellation of the vessels, giving them an onion-peel appearance.

primary disease, such as tuberculosis or multiple myeloma, to classify the amyloidosis as secondary to it.

Could the amyloidosis be secondary to periodic disease itself?

Before answering this question, and without going into the clinical aspects, I would like to draw attention to the similarity of the distribution of the lesions in lupus erythematosus and the distribution of the amyloid in these two cases of periodic disease: the involvement of vessels, and the involvement of the serous surface, the spleen and kidneys.

More striking is the morphologic resemblance of the lesions in lupus erythematosus and periodic disease: the inflammatory lesions in the serous membrane, the presence of a "fibrinoid" substance in the serosa during the acute attacks, the hyaline thrombi in some vessels, the wire-loop-like glomeruli, and the onion-peel-like vessels.

All these facts make me pause before I answer this question, and I leave it to the reader to draw his own conclusions as to whether the amyloidosis is secondary to periodic disease.

Having posed this question, I shall review briefly and quote in the following paragraphs some facts about collagen disease and amyloidosis, and their relation, as an introduction to another question which I shall raise at the end of this paper.

The immuno-allergic features of collagen diseases, of which lupus erythematosus is one, have been pointed out by Rich.[6] Since then, accumulating evidence in the literature implicates an antigen-antibody reaction in this group of diseases. Such a reaction has also been implicated in amyloidosis.[7] Mellors et al.,[8] in an article on localizing gamma globulins, showed similarity or relation between amyloidosis and the collagen diseases. Their main contribution is the demonstration of localization of antibodies at the site of the lesions. Wagner's [9] studies on fibrinoid substances and abnormal tissue proteins, including abnormal amyloid, indicate that not all amyloids are alike. Indeed, some of his patients showed electrophoretic patterns similar to that of the second autopsied case of periodic disease.

The abovementioned clinical, anatomic, immuno-allergic and chemical features show considerable overlapping between collagen diseases and amyloidosis on the one hand and periodic disease on the other. Figure 15 illustrates this interrelationship and indicates a strikingly close similarity between periodic disease and disseminated lupus erythematosus in the following points:

1. Involvement of the connective tissue, including the peritoneum, the joints, kidneys, spleen and vessels.
2. Microscopic pattern of the lesions.
3. Disturbance of the globulins in the plasma and the lesions.

Is periodic disease one of the collagen diseases?

In presenting this question, I would like to make the following points:

FIG. 15. A diagram illustrating the overlapping between collagen diseases, amyloidosis and periodic disease; note the striking similarity between lupus erythematosus and periodic disease.

1. Some of the differentiating criteria among the collagen diseases are the differences in the clinical patterns and the differences in the distribution of the lesions and their severity. As in music, where there is the main theme and its different variations, so in collagen diseases, there is the main lesion and the different manifestations according to which the disease is named.
2. I have not used the term "collagen disease" in this article as a wastebasket to include pathologic states of unknown etiology.
3. Our clinical observations and surgical material, as well as this meager autopsy material, suggest that periodic disease is one of the collagen diseases. However, one of the purposes of this paper is to ask those interested in the subject to pool the information available for a final evaluation.

Summary

1. The clinical and anatomic manifestations of periodic disease are briefly reviewed as observed by the staff of the Clinical and Pathology Departments of the American University of Beirut.

2. Amyloidosis was the cause of the "nephropathy" in two autopsied cases of periodic disease that died with renal failure.

3. A clinicopathologic survey of periodic disease is presented, indicating a possible existing relationship between it and the group of collagen diseases.

Summario in Interlingua

Morbo periodic, o peritonitis periodic, es un disordine a causa non determinate que es characterisate per breve attaccos regular o irregular de dolores in le abdomine o alterubi, associate con febre e leucocytosis. Non es clar proque le repetite attaccos de peritonitis non resulta in adhesiones e obtruction intestinal. Certe patientes exhibi, durante le attaccos, proteinuria e microscopic anormalitates urinari. Alteres disveloppa constante anormalitates urinari e nephropathia con edema e disturbation del proteinas seral, incluse le globulinas. Istes mori ab uremia causate per un progressive insufficientia glomerular e tubular.

Nostre examine de appendices e de peritonee specimens bioptic excidite durante tal attaccos al hospital del Universitate American de Beirut confirma le presentia de un acute processo inflammatori afficiente le superficie serosal. A parte le constatationes usual de inflammation acute, le reaction es characterisate per le presentia de mastzellen, un alte concentration de proteina in le fluido edematic, e sparse depositos de fibrina.

Es opinate que le sparsitate de fibrina, associate con le presentia de mastzellen que cognoscitemente contine heparina, explica le absentia del substruction pro le disveloppamento de adhesiones e le subsequente obstruction intestinal.

Studios histopathologic in specimens necroptic ab duo patientes qui disveloppava nephropathia e disfallimento renal demonstrava grados considerabile de depletion del parenchyma del renes, adrenales, e splen in consequentia de marcate depositiones amyloide. Le afficite glomerulos e vasos renal esseva reminiscente del glomerulos a ansa de filo metallic e del vasos a "pelle de cepa" que es vidite in lupus erythematose. Amyloide esseva etiam presente in omne le vasos del organos alimentate per le axe celiac, sed sin depletion de lor parenchyma. Le depositiones in le peritoneo e le

mucosa intestinal esseva marcatissime. Le corde e le musculos skeletic habeva remanite libere de amyloide. Ben que le deposition amyloide es possibilemente secundari a morbo periodic, le peculiaritate de su distribution in le duo casos necropsiate merita esser mentionate specialmente. Ilo combinava characteristicas de amyloidosis primari e de amyloidosis secundari sin coincider con le un o con le altere.

Le causa del nephropathia e del insufficientia renal que se disveloppa in morbo periodic es amyloidosis renal. Isto, al minus, esseva le caso in le duo patientes necropsiate qui forma le base del presente reporto.

Le observationes clinic e le constatationes anatomic in nostre casos de morbo periodic es interessante e stimula a specular si il existe un relation inter morbo periodic de un latere e amyloidosis e morbos collagenic del altere. Tal speculationes relative al natura de morbo periodic es basate super le sequente punctos:

1. Le peculiaritate del distribution de amyloide.
2. Certe studios que suggere le existentia de un relation inter amyloidosis e le gruppo del morbos collagenic.
3. Le similaritate del distribution de amyloide in le duo casos reportate con le distribution del lesiones in lupus erythematose—le affection del histos conjunctive, incluse le articulationes, le peritoneo, le renes, le splen, e le vasos.
4. Le similaritate microscopic del lesiones in lupus erythematose de un latere e in specimens necroptic e in specimens bioptic obtenite durante le attaccos acute in le duo casos hic reportate del altere latere: Glomerulos a ansa de filo metallic, vasos a "pelle de cepa," e serositis con precipitation de proteina.
5. Le comparation del disturbationes de globulinas in le plasma e del lesiones characteristic de morbo periodic, de amyloidosis, e de lupus erythematose.

Viste que le deposition de amyloide es reversibile, il es postulate que amyloidosis debe esser expectate in patientes con sever morbo periodic si le attaccos que illes suffre es sever e frequente, proque in tal casos le materia deponite durante le recidivas non pote esser resorbite completemente durante le remissiones.

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THE NATURE OF ITCHING IN DERMATITIC SKIN *

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INTRODUCTION

THE purpose of this paper is to present a controlled study of pruritus in dermatitic skin. Recent experimental work has greatly enlarged our knowledge of this troublesome sensation in normal human subjects. A summary of this work will explain the new testing methods developed for use in this report, as well as provide a background understanding of itching mechanisms and responses.

Until recently, histamine was the standard material for experimentally inducing a measurable pruritus. The patient's sensitivity was determined by finding the threshold dilution. Indeed, many workers, following Sir Thomas Lewis, considered histamine as the probable direct chemomediator of clinical pruritus. Gross pruritus had also been produced experimentally by rubbing itch powder into an area of skin, but quantitation and qualitation were impossible by this method. The whole subject of chemomediation of itching was reopened by Broadbent's discovery [1] that itch powder, the tiny, needle-like spicules covering the seedpod of *Mucuna pruriens* (cowhage), could be inactivated by boiling. Itch powder had hitherto been considered to cause itching by penetrating the skin and mechanically stimulating the nerve endings. Broadbent's work suggested the intriguing possibility of finding a new chemomediator of pruritus, and led us to attempt isolation of the substance he had presumably denatured. We were able to demonstrate [2] chromatographically that the active pruritogenic agent in itch powder was a proteinase. The fact that a proteinase could cause pruritus then led us to examine the available purified proteolytic enzymes from this standpoint. This investigation showed that the subepidermal introduction of small quantities (0.01 ml.) of high dilutions (1:1,000 to 1:100,000) of all endopeptidases [3] active in the physiologic pH range produced severe and long-lasting pruritus entirely comparable to the most severe clinical itching. Of this group, crystalline lyophilized trypsin has proved most useful for testing.

Pruritus induced in this manner was accompanied by some urticaria, so that proteinase might still be considered as only another way to cause histamine release. This question was resolved by an experiment in which de-

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natured itch powder spicules were used as tiny injecting needles. Spicules were prepared by drying some in serial dilutions of proteinase, and others in serial dilutions of histamine. When these were rubbed into the skin it was found that proteinase-impregnated spicules could be prepared which would cause intense pruritus without any visible change in the skin (i.e., no urticaria), whereas histamine-impregnated spicules, too weak to cause any itching, still caused grossly visible urticaria. With the demonstration that proteinase, unlike histamine, could cause itching without skin changes, it became possible to theorize on the role of proteolytic enzymes in clinical pruritus. Proteases are available to the subepidermal cutaneous nerve end-

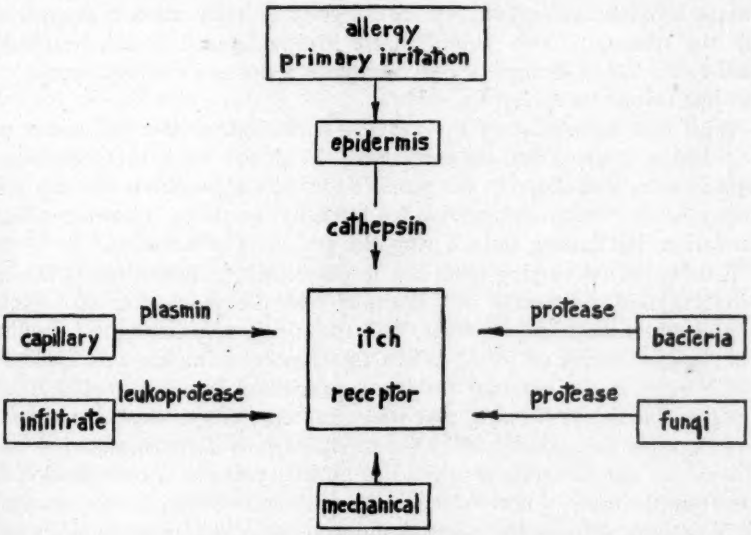


FIG. 1. Proposed common role of endopeptidases in cutaneous production of clinical itching. Mechanical stimuli are unique in acting directly on the subepidermal itch receptor network.

ings from a wide variety of sources in cutaneous disease—from infiltrates (leukopeptidases), from surface flora (fungal and bacterial proteinases), from the capillaries (plasmin), and from damaged epidermal cells (cathepsins). The antigen-antibody reaction has been shown by Ungar [4] to release proteinases. The authors and others have demonstrated that proteinases from these different sources can cause pruritus, that dilute proteinase solutions applied to the surface of dermatitic (broken) skin can cause pruritus, and that proteinase levels are elevated in some pruritic disease.[5] Figure 1 summarizes our present theory of the possible key role of proteinases as the chemomediators of pruritus in many clinical dermatoses. The position of direct mechanical stimulation of the nerve endings has been well established

by other workers, and is included in figure 1. The short duration of mechanically induced itching, compared with that induced by proteinase, should be noted.

The well known punctate nature of the cutaneous sensory system had been demonstrated by mechanical stimulation to hold true for the itch receptors.[6] Once the authors recognized the remarkable uniformity of impregnation of the single cowhage spicule (i.e., that each spicule was "active"), and the minute (0.5 mm.) diameter of its area of action, they were able to confirm the existence of "itch points" by chemical stimuli. By this means the density of itch points could be mapped on different areas of the body, and, conversely, the proportion of single spicules producing pruritus could act as an index of the integrity of innervation in comparison with the normal. "Itch points" were also examined histologically and found to consist of clumps of free, unmyelinated nerve endings spread at a level just below the epidermis.

With this knowledge of the nerve distribution, a micro-electrode was devised to be inserted into the epidermis. With the use of this technic with a square wave stimulator it was possible to find and stimulate the itch point directly, with results comparable in intensity to those following chemostimulation, but lasting only during the period of stimulation.

A delay period varying from five to 60 seconds in length exists between introduction of proteinase or histamine and the perception of pruritus. With electrostimulation, however, this stimulus-perception time is reduced to about one second or less. When this type of stimulus was applied to an itch point in the external ear canal, pruritus followed stimulation with no perceptible delay, showing that when an itch point is stimulated there is no measurable time consumed by the mechanism of electrostimulation itself. If, however, the electrode is applied to an itch point at a considerable distance from the brain, a noticeable stimulus-perception delay begins to appear, and is proportionate to the electrode-brain distance. If a meter segment is measured from toe to hip, the difference in stimulus-perception times for itching at these two points is consistently found to be about 0.5 second. This figure is taken by us to include actual peripheral nerve conduction time. Thus, the data are compatible with the view that the stimuli travel at a rate of about 2 meters per second. This rate corresponds to the conduction speed for the small, unmyelinated "slow (C) fibers."[7] These results were confirmed by mechanical stimulation of itch points. No evidence was found by us to suggest that pruritus is conducted on fast fibers.

With the use of the technics of chemostimulation described above, qualitative and quantitative comparative studies of experimentally induced pruritus were made at various anatomic sites on a number of normal subjects. The results not only confirmed the wide variation of regional sensibility to itch stimuli, but also emphasized the great range of variability of sensitivity in the normal, between individuals as a whole, and from region

to region in the same individual. This randomized variability in itch sensitivity is entirely in agreement with Tomasch's [8] findings of wide variations in the relative proportion of C fibers in peripheral nerves.

For the present study the methods developed and standardized from our experience with normal subjects were applied to the study of common itchy dermatologic conditions at typical sites of cutaneous involvement.

Methods

1. *Subjects and Controls:* Five patients with atopic dermatitis and five randomly selected normal controls were tested in the antecubital fossa. Five other patients with dermatitis of the hands (contact dermatitis, eczema, id reaction) and five other controls were tested on the lateral surfaces of the fingers.

2. *Conditions:* Patients were tested only in areas of grossly dermatitic skin. A clinical history was taken of each patient, with special attention to pruritus. Normal subjects were chosen who had no history of chronic dermatitis or pruritus. Testing was conducted in a warm room. The subjects were instructed to recognize and report only a definite itch localized to the test site. Each test was performed at a site at least 0.5 cm. away from any previously used site.

3. *Itch Sensitivity (Trypsin):* Serial dilutions (1:10,000 to 1:5,000,000) of freshly prepared crystalline lyophilized trypsin (Worthington Biochemical Corp., Freehold, N. J.) were made in 0.9% sodium chloride (Merck, biological) solution. These were kept in an ice bath and injected within a few minutes of preparation. The same commercial lot of enzyme was used for testing each group of patients and controls. Two one-hundredths of a milliliter was injected into the skin as superficially as possible (just below the epidermis), using a tuberculin syringe and a No. 27 needle. Dilutions containing the lowest concentrations of trypsin were injected first, followed, if necessary, by those of higher concentration until a distinct itch was produced which lasted at least 30 seconds. The dilution producing this effect was designated the itch sensitivity to trypsin. Control was achieved by the injection of more dilute proteinase solutions or of normal saline solution.

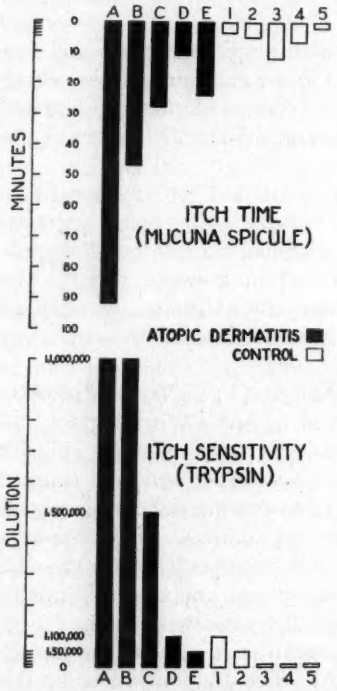
4. *Itch Time (Mucuna spicule):* Single active spicules of *M. pruriens* were inserted one at a time vertically into the skin, using jeweler's forceps under a low power binocular microscope. Whether or not itching resulted, only five spicules were inserted into each subject. The duration of itching caused by each spicule was recorded in minutes, and the sum of these times was designated as the itch time for that subject.

Results

1. *Atopic Dermatitis:* The results of testing are presented graphically in figure 2. The control group, with some individual variations, had a low

sensitivity to proteinase and short total itch time. If this group is compared to the hand control group (figure 3), it is apparent that in normals the antecubital fossa is not a very "itchy" area.

This area, however, was chosen because it is a classic site of dermatitis and pruritus in atopy. The patients differ from the controls in presenting a spectrum of consistently increased sensitivity to itch stimuli, from levels



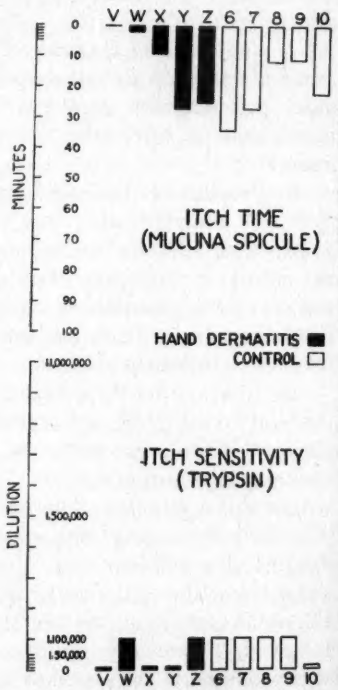


FIG. 2. (*left*) Atopic dermatitis. Itch time and itch sensitivity of five patients with atopic dermatitis (A–E), compared with five normal controls (1–5). The antecubital fossa was the test site.

FIG. 3. (*right*) Hand dermatitis. Itch time and itch sensitivity of five patients with dermatitis of the hands (V–Z), compared with five normal controls (6–10). The lateral surface of the fingers was the test site.

slightly above high normal to levels showing extreme sensitivity to trypsin and extremely long total itch times. In an area not normally "itchy," these patients itch readily and for a long time.

2. *Dermatitis of the Hands:* The results are shown in figure 3. The control subjects illustrated the same general uniformity of response as did the controls in the antecubital fossa group. However, a general difference in area sensitivity was apparent. The hands were much more "itchy" than was the antecubital fossa. Normal itch sensitivity was higher and total

itch times were longer. It can be seen from the graph that the patients' itch responses were normal or subnormal. Although they had a dermatitis in an "itchy" area, their skin had not become more sensitive to itch stimuli. Total itch times are seen to vary widely and without pattern (0 to 27 minutes), but the highest totals do not exceed high normal values. This group was selected to represent various examples of the clinical problem of pruritus, and are considered individually below.

Case Reports

Case V. This woman had chronic dermatitis with recent exacerbations. Her fingers were markedly edematous, erythematous and excoriated, and covered with small, confluent vesicles. Four days prior to testing she had begun a two-day episode of severe intractable pruritus of the hands and had scratched them severely. For two days following this she had experienced little or no itching. In the testing, she had no itching following the insertion of five spicules. At a dilution of 1:10,000 she felt slight itching of minimal duration. Thus, while this patient had recently experienced severe pruritus, at the time of testing she was in an anpruritic state. We feel that her severe dermatitis, combined with extensive excoriation, had damaged the subepidermal nerve receptors to such an extent that no itch point could be found by the single spicule method, and only a weak itch response was felt over the much larger active radius of proteinase injection.

Case W. This woman had contact dermatitis (detergent) in the early healing phase. There were healing vesicles, scaling, subsiding erythema and edema, with slight, occasional pruritus. This case presents a stage of involution further advanced than that of case 1. She had very little response to the spicules but did respond to dilute trypsin. We feel that this indicates early recovery of the receptor network.

Case X. This patient had acute contact dermatitis (laboratory chemicals) two days after onset. Testing was performed in patches of recent vesicles. Slight pruritus was experienced clinically by the patient at this time, but much less than had been experienced in the earlier phases of eruption. His low total itch time and poor response to trypsin indicate that vesiculation was reducing his receptivity to stimulation by damage to the subepidermal network.

Case Y. This man had chronic eczematous dermatitis localized to three fingers three weeks after an acute vesicular phase with severe itching. There was very little pruritus at present, the lesions being 75% healed. The test results were similar to the control findings. However, when this patient had been tested in the early pruritic stage of acute flare, 0.01 ml. of 1:2,000,000 trypsin injection superficially in normal saline solution had caused severe pruritus which lasted for 40 minutes. At this time also, 0.5 c.c. of 1:100,000 trypsin applied topically to the surface of his dermatitic skin caused pruritus which lasted 10 minutes.

Case Z. This patient had an id reaction of the dorsal and palmar surfaces following contact dermatitis (rhus) of the legs. There were scattered, deep-seated vesiculation and moderate pruritus. The threshold was within control limits and, with the use of the criterion of reporting as total itch time only itching localized to the area of stimulation, total itch time was also within normal limits (25 minutes). However, shortly after the introduction of several of the spicules, the patient began to experience itching over a wide area of adjacent dermatitic skin on the test hand. No mechanical stimulation of this area was involved. This "spread" phenomenon lasted for a total of 27 minutes after the itching was no longer distinguishably localized to the area of spicule insertion. Thus the total duration of itching, both

localized and "spread," was 52 minutes. The occurrence of "spread" seems to be confined to patients complaining of moderate to severe pruritus clinically. For example, another patient, with extremely pruritic nummular dermatitis was able to distinguish itching localized to an area of single-spicule insertion on the fourth digit for six minutes, but complained of severe "spread" itching in a large nummular plaque on the thenar area for 35 additional minutes.

Comment

Itching is the most common symptom and often the most vexing therapeutic problem in dermatologic practice. Much clinical information about it already exists: some diseases are known to be "itchy," some are not; some persons with "itchy diseases" (i.e., lichen planus) itch, some do not; few patients who itch complain of itching all the time—the itching "comes and goes," often without apparent relation to the appearance of the lesions; healing lesions are more "itchy"; seemingly acute lesions may not itch; some patients itch "just here", some "all over." This apparent confusion causes many pitfalls in evaluating antipruritic therapy in patients.

These tests were designed to furnish a more controlled and accurate understanding of the phenomenon of itching in patients with dermatologic disease.

Other methods of testing have been evaluated by the authors and rejected in favor of the combined testing procedure used here. Histamine liberators such as "48–80" or morphine [9] not only depend in part on the variable factor of mast cell density in the skin, but also may produce sensitization, or provoke an allergic reaction in sensitized subjects. Gross application of cowhage is a crude tool in comparison to the single-spicule technic; pain may be produced, the skin is irritated, and the possibility of error due to scattering of the material is great. In addition, each of these methods has the disadvantage of offering at best only a limited amount of information. For example, a histamine threshold alone would not have given the true picture of case 1 which was obtained by our combined technic.

We feel that trypsin introduced subepidermally is a physiologic stimulus applied at the area of innervation, and that it reflects the irritability or sensitivity of the cutaneous nerve network over a considerable area encompassing a number of itch points. The total itch time is a method of evaluating the integrity of single "itch points," as well as an index of their density in an area. These impressions have been corroborated by our work with the more elaborate technic of single and multiple electrodes and square wave stimulators.

The results for the patients with atopic dermatitis show that an area of skin not normally very sensitive to pruritus has been converted by this disease to one that is consistently highly sensitive to pruritogenic stimuli. The cutaneous innervation remains intact throughout these areas of lichenification, as indicated by the total itch time. These findings provide an objective basis for these patients' clinical complaints of severe and chronic pruritus;

they perceive stimuli which are totally inapparent to the normal. This fact must be borne in mind by those who wish to emphasize psychosomatic factors in this disease.

In contrast to this group, dermatoses of the hands are shown to occur in a naturally "itchy" area. The eczematous eruption does not produce a persistently "itchy" skin. The itch responsiveness of these patients was remarkable only in the early acute phase of eruption. At other times it was merely consistent with the normal sensitivity of the area. The total itch time was frequently lowered, reflecting damage to the receptor nerve network following acute exacerbation or excoriation, and in these cases the patient may itch very little or not at all.

The phenomenon of spread following a pruritogenic stimulus is not confined to dermatitis of the hands. The "spread phenomenon" seems to suggest that a threshold chemostimulus at a focal point can cause perceptible pruritus in adjacent dermatitic areas where there may be just subthreshold activity at nerve endings. This phenomenon must be distinguished from so-called "spontaneous itching," [10] which is merely pruritus elicited by minor mechanical stimulation of low-threshold skin.

Clinical evaluation of antipruritic therapy in dermatitis of the hands is most difficult, since many phases may be anpruritic due to damage of the nerve receptors for itch. In contrast, in atopy the therapist is presented with a consistent problem of pruritus. Atopic dermatitis is the disease par excellence of itching, and deserves to be the real clinical proving-ground for antipruritic drugs.

Summary and Conclusions

The present state of knowledge about pruritus was reviewed. The itch sensitivity and itch time for patients with atopic dermatitis and dermatitis of the hands were compared with findings for normal subjects. The skin in atopic dermatitis was found to itch more readily and for a far longer time than did normal skin. Although the hands were found to be an area naturally sensitive to itch stimuli, great variations in pruritus were shown to occur in dermatitis of the hands. The phenomena of spread and anpruresis were described. The implications of these findings for management, therapy and drug-testing of clinical pruritus were discussed.

Summario in Interlingua

Recente studios experimental ha monstrate que le prurito causate per *Mucuna pruriens* es debite a un proteinase, i.e. mucunaina, introducite in le pelle per le spiculas del planta. Altere studios ha demonstrate que varie purificate endopeptidases ha le capacitate de causar prurito post lor introduction in le region del rete de nervos subepidermic. In plus, tal pruritos non es associate con ulle visibile alteration del pelle. "Punctos pruriente" representa concentrationes de "libere terminos" de fibras fin, e experimentos physiologic ha indicate que fibras C (i.e. fibras lente) transmitte le sensation de prurientia ab le peripheria. Le presentia de proteinases in morbos

cutanee del typo con prurito ha inducite le autores a postular que proteinases ha un rolo physiologic in le causation de prurito clinic.

In le presente studio le autores ha usate proteinases pro disveloppar tests-standard pro sensibilitate a prurito in pelle normal e in pelle morbide. Le limine de sensibilitate del receptores de prurientia es testate per medio del injection de un solution de trypsina crystallin, durante que le densitate e le grado de damnification del rete nerval es determinate per le insertion de spiculas individual de mucuna. Iste methodos de testation esseva applicate al pelle de patientes con dermatitis atopic e con dermatitis per contacto in le manos, e le resultatos esseva evalutate per comparationes con le valores obtenite in normal subjectos de controlo. In patientes con dermatitis atopic tanto le tempore de prurientia como etiam le sensibilitate pro illo esseva marcatemente augmentate. Isto indicava le presentia de un intacte e hypersensibile rete nervose. Le importantia de iste methodos e lor resultatos es discutite con respecto al testation de nove drogas antipruritic e le therapia de prurito clinic.

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CASE REPORTS

NONTROPICAL SPRUE AND FUNCTIONING ISLET-CELL ADENOMA OF THE PANCREAS: REPORT OF CASE *

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NONTROPICAL sprue is not a common disease, and a functioning islet-cell tumor of the pancreas is rather uncommon. The occurrence of these two conditions in the same patient must be extremely rare because we have been unable to find any such case recorded in the literature. We have encountered such a patient in whom the symptoms of sprue had been noted for about four years, whereas those of the islet-cell tumor of the pancreas had been present for only eight months. This case of nontropical sprue and functioning islet-cell adenoma of the pancreas is being reported to emphasize the significant aspects of diagnosis and treatment.

CASE REPORT

A 51 year old housewife registered at the Mayo Clinic on September 8, 1953, complaining of periodic diarrhea since 1949, and spells of dizziness or weakness when hungry in the eight months prior to registration. She had always been constipated until the fall of 1949, when she had experienced diarrhea for two months. Subsequently she had suffered from attacks of diarrhea lasting about one week three times each year. She said that the stools had a foul odor, were gray or yellow and frothy, and seemed to increase in number with intake of fatty food. Four weeks before admission an episode of diarrhea had begun which was marked by as many as four movements in an hour and continued even at night. The patient also had noticed mild abdominal cramps, bloating, and passage of flatus. Symptomatic treatment had been of no avail.

In the last eight months on arising in the morning she had experienced a feeling of weakness and dizziness which was relieved by eating breakfast. This symptom could be prevented if her husband served her breakfast in bed. She had had the same symptom a few times before lunch or dinner if she had been working hard. The day before admission she had awakened early with severe diarrhea. Two hours later she had noted weakness and dizziness, and then mental confusion so severe that without help she was unable to obtain anything to eat.

She had lost six pounds during the preceding month in spite of a good appetite. During the last six years she had been easily fatigued, and deeply pigmented areas

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had appeared on her face in the last two years. Pigmented dermatitis on the anterior aspects of the legs had been noted in January, 1951.

Physical examination at the clinic revealed asthenia, an appearance of chronic illness, and peculiar pallor and blotchy pigmentation of the face. Her temperature was 98.6° F.; pulse rate, 84 per minute; blood pressure, 100/60 mm. of Hg. The abdomen felt "doughy" on palpation but presented no other abnormality. An area of scaly, pigmentary dermatitis was present on the dorsum of the right foot and ankle.

Laboratory Studies: Examinations and tests of blood produced counts of 3,840,000 erythrocytes and 6,800 leukocytes per milliliter, and 13.1 gm. of hemoglobin

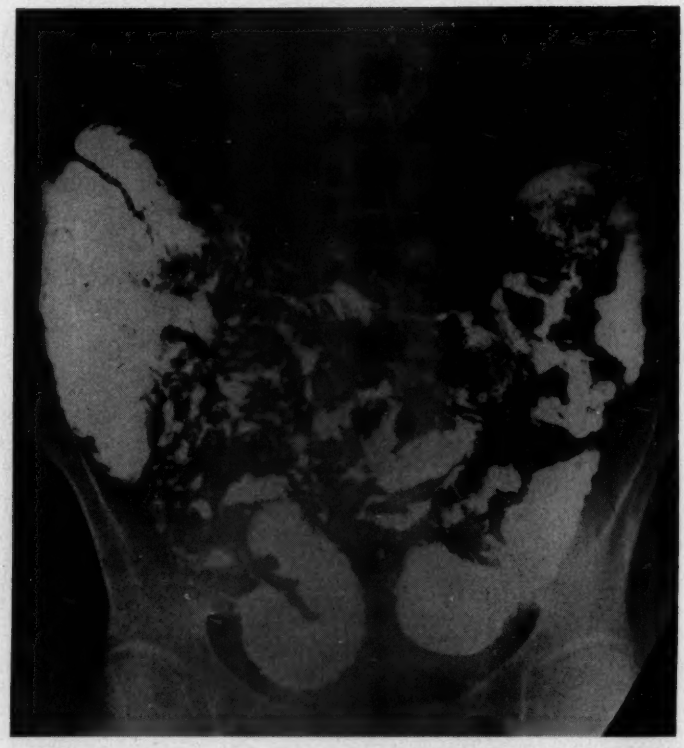

FIG. 1. Deficiency pattern in roentgenogram of small intestine made September 18, 1953, showing puddling, segmentation, and coarsening of mucosal folds.

per 100 ml.; the blood smear showed normocytes, and the sedimentation rate of erythrocytes was 23 mm. in one hour (Westergren method). Urinalysis and a roentgenogram of the chest gave normal results. The value for blood sugar determined 15 hours after the last meal was 43 mg. per 100 ml. At this time the patient evidenced mental confusion and slowness of physical action. Values for serum electrolytes and blood urea were normal. Findings from the bromsulfalein test of liver function (5 mg. of dye per kilogram of body weight) were normal. The value for total serum proteins was 5.8 gm. per 100 ml., with an albumin-globulin ratio of 3.9:1.9. Prothrombin time was 22 seconds (normal, 17 to 18). The concentration of serum calcium was 8.8 mg. per 100 ml. (normal, 9.4 to 10.5).

A stool examination was negative for parasites, and stool cultures contained only the usual flora. Quantitative studies of the stool collected for a two-day period when the patient was following a diet including 100 gm. of fat and 19 gm. of nitrogen revealed steatorrhea by an excretion of 25.9 gm. of fat and 2.9 gm. of nitrogen per day. The total fat excreted represented 56.2% of the total solids. Findings of proctoscopic examination were normal except for minimal hemorrhoids. Roentgenograms of the pancreatic region and skull, and a cholecystogram, evidenced normal conditions. Roentgenologic study of the upper part of the gastrointestinal tract after ingestion of barium indicated normality of the stomach and duodenum, but changes noted in the jejunum and ileum were suggestive of a deficiency pattern consistent with sprue (figure 1). The oral glucose tolerance test produced a flat curve with values of 83 mg. per 100 ml. initially, 115 at one hour, 90 at two hours, and 95 at three hours. Analysis of the gastric secretions after subcutaneous ad-

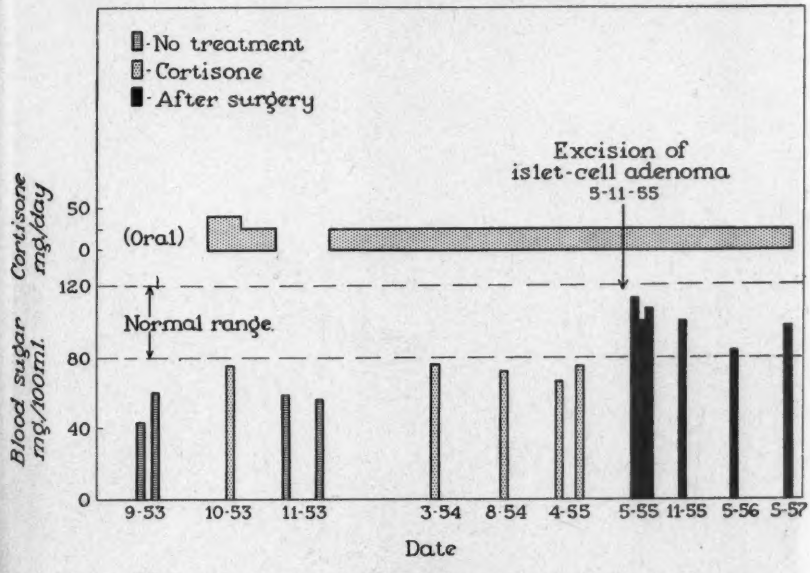

FIG. 2. Effects of cortisone and of surgical removal of an islet-cell adenoma on blood sugar levels.

ministration of histamine showed 22 units of free hydrochloric acid. Duodenal drainage contained cloudy yellow bile; the concentrations of pancreatic amylase, lipase and trypsin were normal, and the pH was 6.9.

The basal metabolic rate was plus 20%, and the protein-bound iodide was 3.0 μg per 100 ml. of blood. The 24-hour urinary excretion of 17-ketosteroids was 1.2 mg., and of corticosteroids, 0.76 mg. After the intravenous administration of 25 mg. of ACTH (adrenocorticotropin) for two days, these values were 2.1 mg. and 2.46 mg., respectively.

The effect of fasting on the level of blood sugar was determined on two occasions (tests 1 and 2 in the table), and values of 38 mg. per 100 ml. after 19 hours and 35 mg. per 100 ml. after 47 hours were found. In each instance weakness, sweating, mental confusion and incoördination developed. The symptoms were promptly relieved by glucose given intravenously, or by oral feeding.

Course: It was concluded that this patient probably was suffering from nontropical sprue and hyperinsulinism owing to an islet-cell adenoma of the pancreas, although sprue alone might explain all of her symptoms. She was given a sprue type of diet, with restricted fat, a multivitamin capsule, vitamin B_{12} by mouth, folic acid, water-soluble vitamins K and D, parenterally administered liver extract, and cortisone (12.5 mg. by mouth three times a day and later twice a day).

On this program the patient seemed to improve. The diarrhea ceased; she had only one soft stool daily and gained weight (106 to 116 pounds). The scaly dermatitis on the right foot and pigmentation of the face diminished. She had no symptoms of hypoglycemia except during one month in which administration of

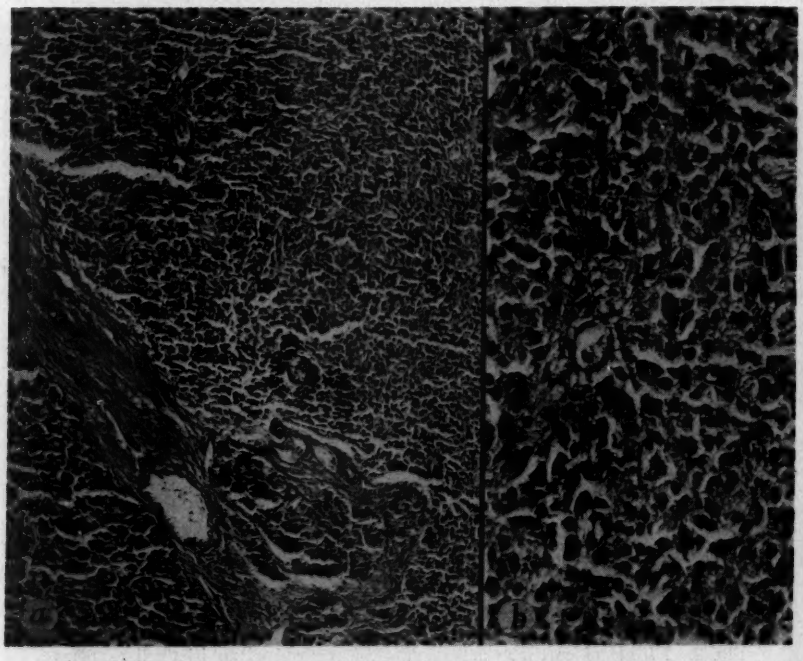

FIG. 3. Microscopic appearance of islet-cell adenoma (hematoxylin and eosin stain). *a.* Normal pancreatic tissue in lower left and adenoma on right separated by connective tissue (× 100). *b.* Adenoma (× 300).

cortisone was discontinued. After 18 months, while still receiving cortisone, the patient was instructed to fast and a blood sugar level of 38 mg. per 100 ml. at 62 hours was found (test 3, table). At this time she suffered from symptoms of mental confusion and right hemiparesis, which promptly disappeared with the intravenous administration of glucose. The variations in blood sugar level with no treatment (except the supportive measures mentioned above) and with the addition of cortisone are shown in figure 2.

Since these observations seemed to demonstrate that the patient did have a functioning islet-cell tumor of the pancreas, surgical exploration of the pancreas was advised. She was prepared by the intramuscular administration of 200 mg. of cortisone daily for three days, and operation was performed on May 11, 1955. A

small adenoma was palpated in the head of the pancreas and was excised. The tail of the pancreas felt nodular and, because of the possibility of other lesions, this portion of the pancreas and the spleen were removed also. The liver, small intestine and colon appeared normal. The pathologic report described an islet-cell adenoma (0.6 cm. in diameter) from the head of the pancreas (figures 3*a* and *b*) and normal pancreatic tissue in the tail.

After operation the patient was given decreasing amounts of cortisone parenterally for four days, and since then has taken 12.5 mg. orally twice a day. She has continued to follow the sprue program described. The fasting blood sugar

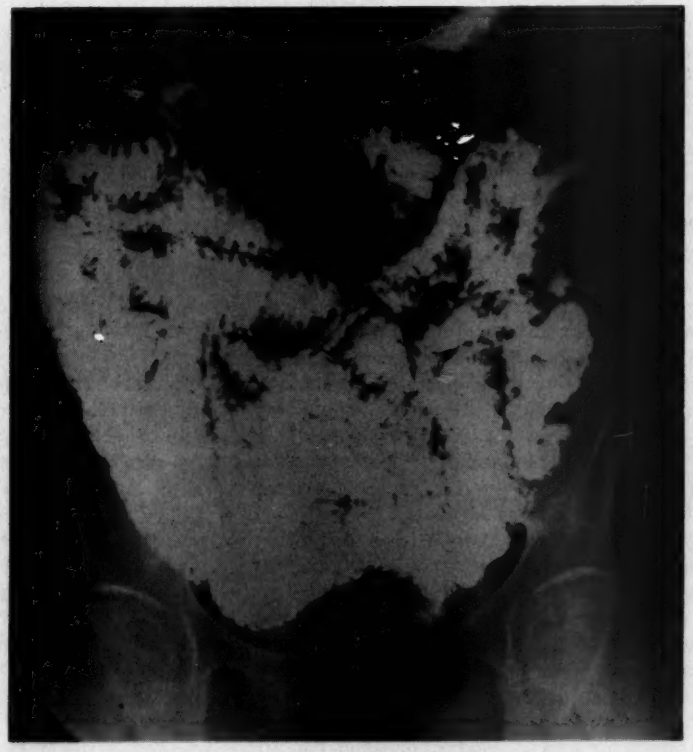

FIG. 4. Small intestine on June 5, 1956; less evidence of deficiency changes than in 1953 (figure 1).

values have varied from 84 to 113 mg. per 100 ml. (figure 2), and no symptoms of hypoglycemia have appeared. The patient's general condition has been good, her weight has been maintained, and she has been able to carry on all her household duties. Her bowel movements are regular and stools are formed, unless she happens to eat fat in excess of the dietary allowance, after which a temporary diarrhea is noted. The value for hemoglobin has ranged from 11.2 to 11.9 gm. per 100 ml. of blood. In May, 1956 and 1957, prothrombin times and concentrations of serum calcium were normal. Roentgenologic study of the small intestine after administration of barium in June, 1956, revealed evidence of deficiency, but less marked

TABLE 1

Effect of Fasting on Blood Sugar Level in Three Separate Tests

Fast	Date	Previous Treatment	Minimal Blood Sugar, Mg./100 Ml.	Duration of Fast, Hr.	Symptoms*
1	9-11-53	None	38	19	Weakness, sweating, mental confusion
2	9-23-53	None	35	47	Sweating, mental confusion, poor muscle coördination
3	4-23-55	Cortisone, 25 mg. daily by mouth	38	62	Sweating, mental confusion, temporary right hemiparesis

* Symptoms were promptly relieved by giving glucose intravenously.

than had been noted previously (figure 4). Attempts to discontinue the administration of cortisone have resulted in return of diarrhea and fatigability.

COMMENT

In this case, diagnoses of nontropical sprue and islet-cell adenoma of the pancreas were established, although at first it seemed possible that nontropical sprue might account for the entire clinical picture.

Our patient fulfilled the diagnostic criteria for nontropical sprue. Definite steatorrhea, a deficiency pattern on roentgenologic study of the small intestine, a flat glucose tolerance curve after oral administration of glucose, hypoproteinemia, hypocalcemia and hypoprothrombinemia were detected. Pancreatic insufficiency and other specific causes for steatorrhea or malabsorption were excluded.

Hypoglycemia, thought to be due to hyperinsulinism, was demonstrated by fasting on three separate occasions. Characteristic symptoms of hypoglycemia developed in the presence of a low blood sugar level each time, and disappeared when glucose was administered orally or intravenously. In our experience, the glucose tolerance test has been of little value in the diagnosis of a functioning islet-cell tumor of the pancreas. In this case it was thought that the flatness of the glucose tolerance curve after oral administration of glucose was due to the presence of sprue. There was no evidence of hepatic disease, hypofunction of the pituitary or adrenal cortex, or other conditions which may cause hypoglycemia.[1, 2]

Significant hypoglycemia ordinarily is not associated with sprue. In sprue the fasting blood sugar level usually is normal or but slightly below the normal range;[3] and the oral glucose tolerance curve usually is flat, probably indicating an absorptive defect in the small intestine. Hypoglycemia may be associated with severe inanition or a history of gastroenterostomy or of gastric resection.[1] One case of hypoglycemia associated with acute gastroenteritis has been reported[4] in which the symptoms of hypoglycemia were accompanied by fasting blood sugar levels of 55, 48 and 58 mg. per 100 ml., and relieved by intravenous administration of glucose. The fasting blood sugar levels were consistently normal after improvement of the gastroenteritis.

In our case, however, after a trial of medical treatment for sprue, it became evident that the patient also had a functioning islet-cell tumor of the pancreas. The procedure of choice, when the diagnosis of hyperinsulinism due to hyperfunctioning islet-cell tissue of the pancreas has been established, is surgical exploration of the pancreas.[5] If a tumor is discovered at operation, it should be completely removed; if a tumor is not found, partial pancreatectomy is usually performed, because about three fourths of the tumors are situated in the body or tail of the pancreas. One reason for concern over delaying surgical exploration of the pancreas is that occasionally a tumor of the islet cells is malignant rather than benign. In one series of 91 cases of hyperinsulinism, adenoma was found at operation in 46, adenocarcinoma, grade 1, in 23, metastasizing carcinoma in seven, and a normal pancreas in 15.[6] Furthermore, hyperinsulinism over a period may be associated with changes in the central nervous system or neuronopathy.[7, 8]

The question arises whether the nontropical sprue and the functioning islet-cell adenoma were of coincidental occurrence or had some causal relationship in our patient. One case of an atypical sprue syndrome associated with a large, inactive islet-cell adenoma of the pancreas, a very small parathyroid adenoma and a small thyroid adenoma has been reported.[9] The level of fasting blood sugar was 114 mg. per 100 ml., and symptoms of hypoglycemia were not present. Two cases of hyperparathyroidism associated with idiopathic steatorrhea or sprue have been described.[10] Probably there are other instances of association between sprue and glands of internal secretion. Whether these relationships are matters of chance or something more specific has not been established.

In the course of treatment, the object of giving our patient cortisone was its possible effect in maintaining normal levels of blood sugar. Cortisone has been shown to be of value in treatment of sprue by improving intestinal absorption or utilization of fat, protein, water and probably carbohydrate.[11, 12] The fasting values for blood sugar in our patient remained just below normal, and she had no symptoms of hypoglycemia during an 18-month period of observation. However, cortisone did not alter the results of the 72-hour fasting test except possibly to delay slightly the onset of hypoglycemic symptoms. Large doses of adrenocorticotropin (ACTH) have been shown to improve fasting blood sugar levels temporarily, but these quickly fall when administration of ACTH is discontinued.[13] Cortisone has been declared of no benefit to one patient with an islet-cell tumor of the pancreas and asthma.[14]

Summary

In a case of nontropical sprue associated with functioning islet-cell adenoma of the pancreas, the presenting symptoms included diarrhea, and spells of confusion, sweating and weakness, relieved by food. The patient was found to have steatorrhea, and possible causes other than sprue were excluded. Hyperinsulinism was demonstrated by eliciting symptoms of hypoglycemia during a fast, with values of blood sugar as low as 35 mg. per 100 ml., then relieving the symptoms by administration of glucose. Treatment with cortisone given orally, a nutritious low-fat diet and vitamin supplements resulted in symptomatic improvement of the nontropical sprue. However, the hypoglycemic effect of fasting persisted. Surgical removal of an islet-cell adenoma from the head of the

pancreas, with continuation of the regimen previously noted, has given complete relief of the patient's hypoglycemic reactions. Attempts to discontinue the use of cortisone have resulted in return of the diarrhea. Various aspects of the association of these two disease entities are discussed.

Summario in Interlingua

Sprue non-tropic non es un morbo commun, e un tumor functionante de cellulas del insula in le pancreas es plus tosto rar. Le occurrentia de iste duo conditiones in le mesme patiente es apparentemente un phenomeno exceptional, proque un revista del litteratura ha producite non mesmo un sol tal caso. Es reportate un caso de sprue non-tropical e adenoma functionante de cellulas insular del pancreas. Illo esseva incontrate al Clinica Mayo. Le objectivo del reporto es sublinear aspectos significative del diagnose e del tractamento.

Le symptomas de presentation in iste caso includeva diarrhea e accessos de confusion, transpiration, e debilitate que esseva alleviabile per le ingestion de nutrimento. Esseva constatate le presentia de steatorrhea. Causas possibile, a parte sprue, esseva excludite. Hyperinsulinismo esseva demonstrate per evocar symptomas de hypoglycemia in stato jejun (con valores pro sucro sanguinee descendente usque a 35 mg per 100 ml) sequite per alleviation del symptomas sub le effecto del administration de glucosa. Un programma therapeutic de cortisona oral, un nutritive dieta a basse contento de grassia, e supplementos de vitamina resultava in un melioration symptomatic del sprue non-tropical. Tamen, le effecto hypoglycemic de jejunos persisteva. Le ablation chirurgic de un adenoma de cellulas insular ab le capite del pancreas—con continuation del supra-notate programma therapeutic—ha resultate in le complete alleviation del reactiones hypoglycemic del patiente. Varie aspectos del association de iste duo entitates pathologic es discutite.

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HEMORRHAGIC DIATHESIS IN CARCINOMA OF THE STOMACH: A CASE REPORT *

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Acute hemorrhagic syndromes may occasionally develop in association with carcinoma of the stomach,[1-4] prostate,[5] pancreas [4] or gall-bladder.[2] Tagnon [6] has demonstrated the presence of a proteolytic enzyme in both normal and malignant prostatic tissue which produces fibrinolysis and bleeding in patients with metastatic carcinoma of the prostate. Recently, Frick [4] reported four cases of carcinoma—two of the stomach, one of the pancreas and one of the prostate—in which hemorrhagic tendencies involved deficiencies of fibrinogen, prothrombin, labile prothrombin conversion factor, and antihemophilic globulin. It is the purpose of this paper to report a case of carcinoma of the stomach complicated by deficiencies of fibrinogen, prothrombin, labile and stable prothrombin conversion factors, and platelets.

Case Report

First Admission: A 39 year old white male entered the hospital for the first time July 16, 1956, complaining of loss of weight, nervousness and vomiting of seven days' duration. The patient admitted periodic drinking for the last 12 years. His dietary intake was good when he was sober. He denied melena, hematemesis, jaundice or exposure to hepatic or bone marrow toxins. He gave no family or personal history of bleeding tendencies.

Physical Examination: The patient was a thin, dehydrated, tremulous white male looking older than his stated age. There was no jaundice, purpura or adenopathy. The liver and spleen were not palpable; no abdominal masses could be felt.

Laboratory Data: Hemoglobin was 12.4 gm.%. The white blood cell count was 13,700; the differential count was normal. Sedimentation rate was 8 mm. per hour. A urinalysis showed no abnormality. Bromsulfalein retention was 2.5% after 45 minutes (5 mg. per kilogram). Three stool specimens gave a 0 to 1 guaiac reaction. Gastric analysis revealed no free acid after histamine. X-ray films of the chest were normal. An upper gastrointestinal series revealed a small ulcer crater on the lesser curvature of the stomach, and a rigid body of the stomach consistent with a linitis plastica type of carcinoma. Gastric cytologic studies were negative for malignant cells. After these studies the patient was discharged from the hospital.

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Second Admission: Two weeks following discharge the patient was re-admitted because of bleeding gums, intermittent fever and low back and thigh pain of about one week's duration.

Laboratory Data: The hemoglobin was 9.7 gm.%. The white blood cell count was 17,900, with 7 metamyelocytes and 1 metarubricyte per 100 white cells. There were 67,000 platelets per cubic millimeter. Sedimentation rate was 2 mm. per hour; bleeding time, 3.5 minutes; clotting time (Lee White), 25 minutes. Clot retraction took place in four hours. There was no lysis of the clot in 48 hours at 37° C., but the clot was soft and friable on cutting. Capillary fragility was marked. Direct and indirect Coombs' tests were negative. Bone marrow aspiration revealed adequate megakaryocytes, hyperplasia of granulocytic and rubricytic series with normal maturation, and an increase in hemosiderin and eosinophils. No abnormal cells were seen. No circulating anticoagulants were detected.[7] Table 1 lists the values for stable and labile prothrombin conversion factors,[8, 9] fibrinogen,[10, 11] and prothrombin.[12] The prothrombin time [13] ranged from 16 to 57% of normal. Total protein was 6.8 gm.%; albumin, 4.1 gm.%; globulin, 2.7 gm.%. There was 9% bromsulfalein retention after 45 minutes. Serum bilirubin was 0.46 mg.%. Cephalin flocculation was 3 plus at 48 hours; thymol turbidity, 2.5 units. Blood cultures were negative. The stools were grossly bloody. Fecal urobilinogen measured 180 mg. per 24 hours (hemoglobin, 5.7 to 7.7 gm.%). An x-ray film revealed minimal fluid at the base of the right lung; x-ray films of the lumbosacral spine showed no abnormalities. An axillary lymph node biopsy revealed nonspecific hyperplasia.

Hospital Course: The patient's 30 days in the hospital were marked by remittent fever, spontaneous purpura, epistaxis, bleeding gums, hematemesis, gross melena, bleeding from the sites of the bone marrow aspiration and the biopsy, and the appearance of increasing numbers of early myeloid and rubricytic cells in the peripheral blood. He required 24 units of blood to maintain the hemoglobin at approximately 8.5 gm.%. Large doses of vitamin K_1 oxide failed to raise the prothrombin concentration. Beginning on the fourth day, prednisolone was administered in doses of 90 mg. daily. There was no clinical or hematologic response in eight days. On the thirteenth day the patient received 10 mg. of nitrogen mustard, but showed no improvement. He died on the thirtieth hospital day.

Autopsy Report: The body was that of an emaciated white male covered with ecchymotic areas. Microscopically, the lungs showed widespread lymphatic infiltration by tumor and vascular tumor emboli. The liver weighed 1,500 gm. and showed no gross evidence of tumor; microscopic evidence of tumor was found in one section of liver tissue. The stomach and lower esophagus were densely infiltrated by an adenocarcinoma. The spleen weighed 250 gm., and was the site of extramedullary hematopoiesis. Several mediastinal and mesenteric lymph nodes were diffusely replaced by clumps of tumor. Sections of bone from the lumbar vertebrae and the iliac crest revealed the marrow spaces to be replaced by fibrous tissue and tumor; there were only rare focal areas of hematopoiesis.

Discussion

The above case is the sixth reported example of an acute hemorrhagic diathesis involving deficiencies of multiple factors of the blood clotting system associated with gastric carcinoma. The data presented in these six cases are summarized in table 2.

The coagulation defect in these patients is complex and is not completely understood. Although hypofibrinogenemia is a consistent finding, it is apparently only one of several important deficiencies. Normal platelet counts have been noted in patients with this acute hemorrhagic syndrome;[14] therefore,

TABLE 1
Studies of Blood Clotting Factors

	SPCF* %	LPCF† %	Fibrinogen mg./100 ml.	Prothrombin %
Normal	70–100	70–100	300–600	70–100
8/10/56	41	34		40
8/17/56	64	35	72	56
8/20/56	62	50	90	71
8/21/56	60	45	58	64
8/24/56	50	34	40	65
8/27/56	56	46	95	60
8/30/56	70	41	52	47
9/ 4/56	83	21.5	23	70

* Stable prothrombin conversion factor.
† Labile prothrombin conversion factor.

thrombocytopenia may be variable or absent. The role of prothrombin factors in the pathogenesis of the bleeding is not clear. Frick [4] found a deficiency of labile prothrombin conversion factor and antihemophilic globulin, but normal stable prothrombin conversion factor and plasma thromboplastin component in both his cases. In our patient the value for the labile conversion factor was low; however, our determinations also gave low values for stable prothrombin conversion factor (table 1), a finding which has not been reported previously to our knowledge. Unfortunately, tests for antihemophilic globulin and plasma thromboplastic component were not performed.

TABLE 2
Summary of Reported Cases

Author	Platelets per cu. mm.	Bleeding Time min.	Clotting Time min.	Prothrombin Time	Fibrinogen mg. per 100 ml.	Clot Retraction	Fibrinolysis	Tourniquet Test
Fleischhacker[1] 1940	60,000	2	Indef. prolonged		40–53	None		Positive
Braun and Horányi[2] 1951	160,000	2	16	65%·	80	Excellent	Transitory fibrinolysis	Negative
Bennike and Mullertz[3] 1952	69,000–170,000	5–30	15–240	>60 sec.	30–80		Normal values for fibrinolytic activity	Negative
Frick[4] Case I 1956	94,000	6	25	70 sec.	26	?		Positive
Frick[4] Case II 1956	122,000	3	25	17 sec.	40	Good	No lysis	Negative
Biben and Tyan 1957	67,000	3-1/2	25	16%	23–95	Present in 4 hrs.	No lysis	Positive

Estimates of the critical level of fibrinogen below which a hemorrhagic state appears vary from 60 to 150 mg. per 100 ml. in patients with congenital afibrinogenemia.[15] This deficit may be compensated for in part by normality of vascular factors, platelets and other coagulation factors.[16, 17] In a 10-year follow-up study Hardisty and Pinniger [16] commented on the slight disability in congenital afibrinogenemia, less so than in hemophilia.[18] In our patient the decrease of labile and stable prothrombin conversion factors, prothrombin, platelets and capillary integrity was sufficiently severe to preclude a possible compensation

for the hypofibrinogenemia. There was no clinical change in bleeding when the fibrinogen value was at the highest reported level (95 mg. per 100 ml.).

The mechanism of the above deficiencies may be inadequate production, intravascular clotting produced by thromboplastic substances, or increased destruction by lytic enzyme(s).

The liver is considered to be the source of the fibrinogen and other proteins concerned in the clotting mechanism, and destruction or removal of this organ is a recognized cause of deficiencies of these factors. Extensive liver damage was not found in any of the above reported cases. Autopsy data, although incomplete in some of these cases, showed no instance of gross metastases, and only occasional evidence of tumor was observed microscopically.

Thromboplastic substances have been noted to cause hypofibrinogenemia by intravascular clotting in some obstetric accidents and disorders.[11, 19] There has been little or no anatomic evidence of this process in cases of bleeding associated with cancer. Thrombi have been noted in some of the vessels at autopsy in patients with carcinoma of the prostate, but they were not abundant.[20]

A proteolytic enzyme capable of digesting fibrin, fibrinogen, labile prothrombin conversion factor and prothrombin has been demonstrated in both normal and malignant prostatic tissue from patients with metastatic carcinoma of the prostate.[6, 14, 21] We were unable to demonstrate fibrinolysin in a clot of whole blood from our patient. Although a "lytic" enzyme(s) could best explain this hemorrhagic diathesis by its effect on fibrinogen, prothrombin and the prothrombin conversion factors, to date no such enzyme(s) has been demonstrated in carcinoma of the stomach.

Summary

1. A case is presented of carcinoma of the stomach complicated by an acute bleeding diathesis due to thrombocytopenia, hypofibrinogenemia, hypoprothrombinemia and decreases in stable and labile prothrombin conversion factors.

2. A brief review of the literature and discussion of possible mechanisms involved are presented.

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Summario in Interlingua

Iste reporto describe un caso de carcinoma del stomacho, complicate per diathese de sanguination acute. Esseva constatate deficientias de fibrinogeno, prothrombina, labile e stabile factores de conversion prothrombinic, e plachettas. Le tractamento remaneva sin effecto. Al necropsia, carcinoma metastatic esseva trovate in nodos lymphatic, osso, e pulmon. In un section de histo hepatic, su manifestationes esseva solmente microscopic.

Simile syndromes hemorrhagic ha essite reportate in casos de carcinoma del prostata, del pancreas, e del vesica biliari. Es presentate un summario de studios hematologic in cinque previe casos de iste syndrome associate con carcinoma del stomacho. Le defecto coagulatori in iste patientes non es completemente clar. Hypofibrinogenemia es un constatation regular, sed illo representa solmente un de plure deficientias. Un reducite nivello de stabile factor de conversion prothrombinic

esseva observate in le patiente del presente reporto. Iste deficientia non es mentionate in previe reportos.

Le mechanismo del deficientias in factores coagulatori es possibilemente un question de production inadequate, de coagulation intravascular, o de destruction per un o plure enzymas lytic. Un enzyma proteolytic, que es capace de digerer fibrina, fibrinogeno, labile factor de conversion prothrombinic, e prothrombina, ha essite demonstrate tanto in normal glandulas prostatic como etiam in maligne histo prostatic ab patientes con carcinoma metastatic. Ben que il existe nulle directe prova que iste mechanismo es interessate in casos de diathese de sanguination acute occurrente in association con carcinoma del stomacho, un enzyma (o plure enzymas) lytic offrerea —per su effecto super fibrinogeno, prothrombina, e le factores de conversion prothrombinic—le melior explication de iste typo de diathese hemorrhagic.

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ANEURYSMAL DILATATION OF THE AORTIC SINUSES IN COARCTATION OF THE AORTA: REPORT OF TWO NEW CASES AND REVIEW OF THE LITERATURE*†

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Angiocardiography has made possible the diagnosis of congenital and acquired unperforated aortic sinus aneurysms.[1-3] The congenital type is apparently much more common than was previously suspected. In arachnodactyly, for example, five cases of aneurysmal dilatation of the aortic sinuses were recently reported, three in adults,[4] and in identical twins, aged two years.[5] Five reports of congenital aortic sinus aneurysms associated with coarctation of the aorta have also been previously published.[6-8] Another with a closely related condition, pseudocoarctation, has also been recorded.[9]

Two new cases of coarctation of the aorta with aneurysmal dilatation of the aortic sinuses are herein described. The purpose of this paper is to review the clinical and roentgen features of aortic sinus (of Valsalva) aneurysms associated with coarctation of the aorta that are useful in establishing the diagnosis.

Case Reports

Case 1. A 26 year old man was first seen in The New York Hospital clinic on February 23, 1956, with complaint of pain in the right thigh of one week's duration. Nine years previously he had had osteomyelitis requiring multiple operations on the right leg, ankle and elbow. Following that he was asymptomatic until the onset of pain in the thigh. Examination disclosed a well developed man, weighing 140 pounds, with fever, hypertension (178/92 mm. Hg), and a small, tender mass over the thigh. Recurrence of osteomyelitis was suspected, and he was referred to the Hospital for Special Surgery where, after treatment with antibiotics, he improved. Examination of the heart revealed a soft systolic (grade 1) murmur at the apex and harsh (grade 3) systolic murmurs over the base of the heart transmitted into the neck. The arm blood pressures were 210/90 and 190/90 mm. of Hg, respectively; the leg pressures were 150/110 mm. Hg. A chest x-ray showed enlargement of the left ventricle, a deformed aortic arch and rib notching of the under surfaces of

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the fourth to eighth ribs bilaterally (figure 1A). The electrocardiogram showed some left ventricular hypertrophy; there was no deviation of the electrical axis. Angiocardiography on July 24, 1956, revealed a large left ventricle; the wall measured 18 mm. (average normal, 10 mm.). There was aneurysmal dilatation of the aortic sinuses, and the ascending aorta was dilated and measured 45 mm. in the mid-ascending portion (average normal, 28 mm.). The innominate and left subclavian

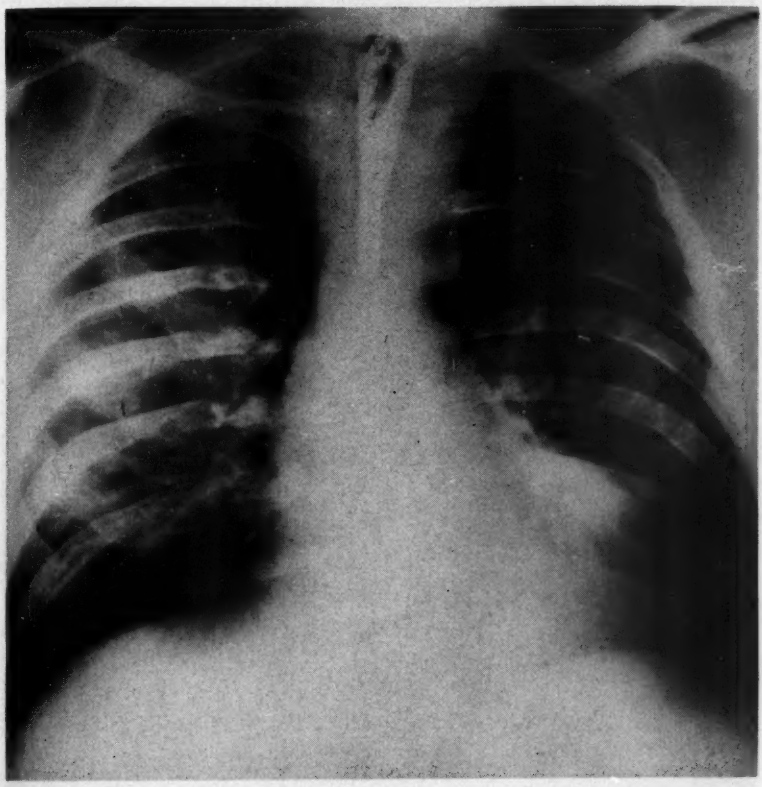

FIG. 1A. *Case 1.* Frontal esophagram shows absence of the aortic knob. The heart is enlarged, especially the left ventricle. Moderate bilateral rib notching of the under surfaces of the fourth to eighth ribs is evident.

arteries were moderately dilated. A point of coarctation was present just beyond the origin of the left subclavian artery, and there were enlarged collaterals (internal mammary and scapula arteries) (figure 1B).

The patient was admitted to The New York Hospital on May 18, 1956, and resection of the coarctation with end-to-end anastomosis of the aorta was performed with hypothermia; recovery was uneventful. Follow-up examination on June 29, 1956, showed the patient to be in good health. The blood pressure, right arm, was 160/70 mm. Hg; right leg, 160/110 mm. Hg. A blowing (grade 3) systolic murmur along the left sternal border from the first to the third interspace, transmitted to the back and loudest above the left scapula, was still present.

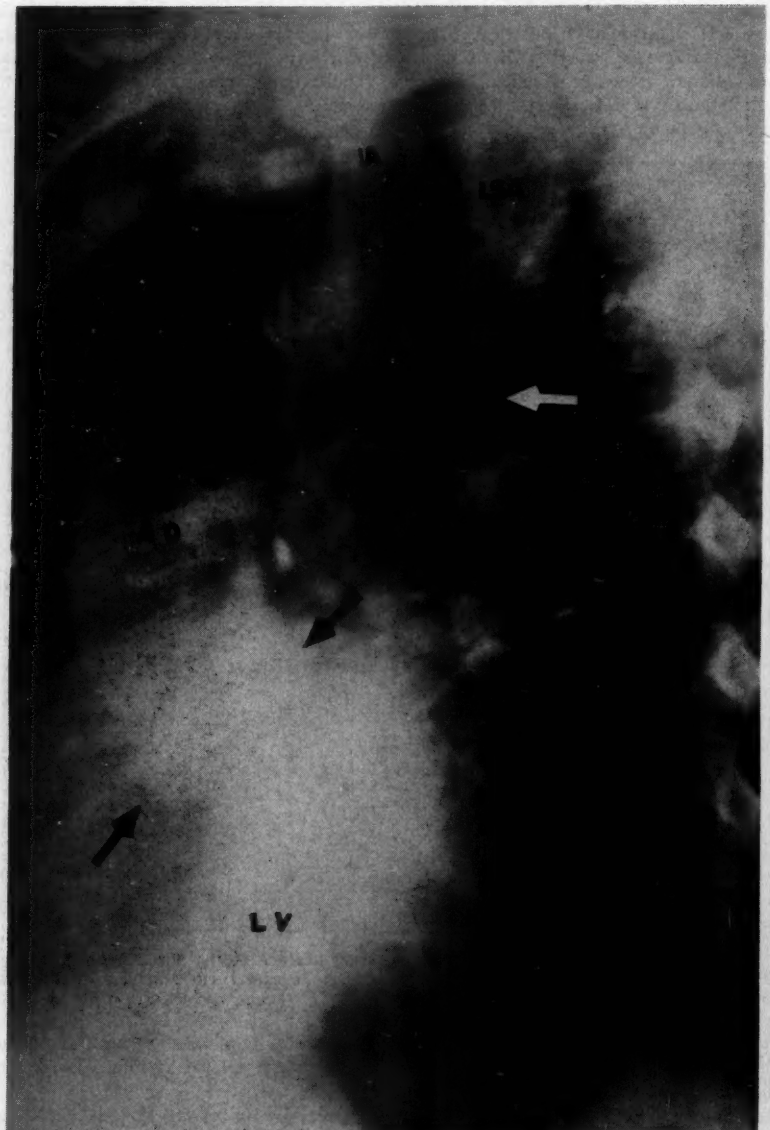

FIG. 1B. *Case 1.* Left anterior oblique angiocardiogram, 8 seconds after the beginning of injection, reveals a large left ventricle (LV); the aortic sinuses (arrows) are aneurysmally dilated, and the ascending aorta (AO), the innominate (IA) and left subclavian arteries (LSA) are also widened. White arrow indicates the point of coarctation of the aorta.

Case 2. A 13 year old asymptomatic schoolboy was found to have hypertension during an examination to determine fitness to engage in athletics. The upper extremity blood pressure was 158/92; the lower, 90/50 mm. Hg. On admission to the United States Naval Hospital, St. Albans, N. Y., on July 23, 1956, he was found to be in good general condition; weight, 114 pounds; height, 66 inches. A systolic murmur (grade 2) was heard over the base of the heart. The murmur was loudest to the left of the upper sternum but was also heard in the axilla and left scapula area.

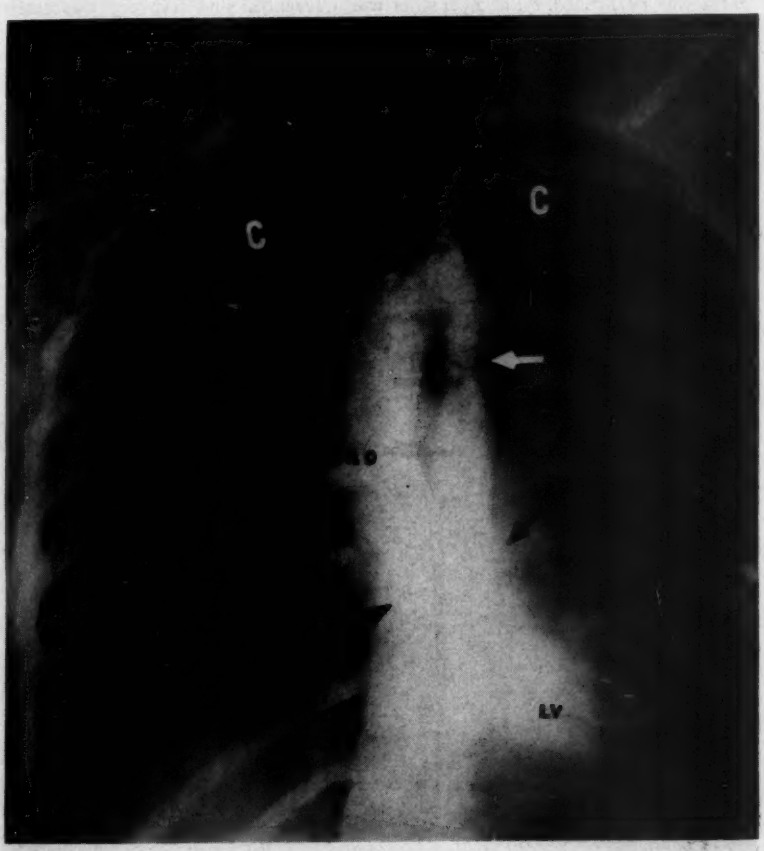

FIG. 2A. *Case 2.* Frontal angiocardiogram shows a normal sized left ventricle (LV). There is aneurysmal dilatation of the aortic sinuses (arrows). The ascending aorta (AO) and the innominate and left subclavian arteries are normal in caliber. Note the point of coarctation of the aorta (white arrow). The mammary arteries (C) are large and tortuous.

The heart was not enlarged. The popliteal and peripheral leg arteries were not palpable. A roentgenogram of the chest (figure 2A) revealed bilateral notching of the under surfaces of the fifth, eighth and ninth ribs. The heart was normal in size and configuration; the aortic knob was hypoplastic. The electrocardiogram was normal. Angiocardiography, performed by Dr. B. P. Sammons in frontal and left

anterior oblique views disclosed slight enlargement of the left ventricular wall (12 mm.), with aneurysmal dilatation of the aortic sinuses. The ascending aorta and brachiocephalic arteries were slightly dilated, the mid-ascending aorta measuring 32 mm. in diameter (average normal, 28 mm.). Coarctation of the aorta just beyond the aortic arch was clearly demonstrated. In addition, there were pronounced enlargement and tortuosity of the internal mammary arteries (figures 2A and B).

On August 20, 1956, resection of the coarctation with end-to-end anastomosis of the aorta was performed. The operation was uneventful and recovery was entirely

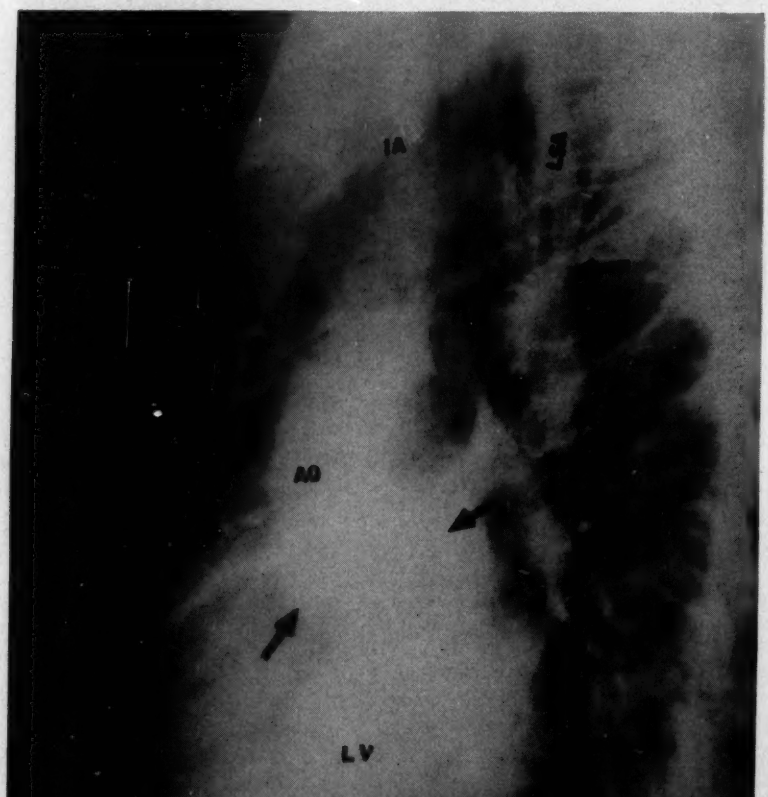

FIG. 2B. *Case 2.* Left anterior oblique angiocardiogram reveals the opacified left ventricle (LV), the aneurysmal dilatation of the aortic sinuses (arrows), the ascending aorta (AO), and the innominate (IA) and left subclavian arteries (LSA). The point of coarctation of the aorta (arrow) is just beyond the origin of the left subclavian artery.

satisfactory, the patient being discharged after 12 days. Return of the pulses to the lower extremities followed, and the blood pressures of both extremities became normal. The systolic murmur over the base of the heart, however, persisted.

Discussion

The Normal Aortic Sinuses: The aortic sinuses are three small dilatations in the wall of the aorta immediately above the valves. Each sinus lies just above the attachment of an aortic cusp. The right and left coronary arteries usually originate within two of the aortic sinuses; however, they may emerge immediately distal to the aortic sinuses. The aortic sinuses and their corresponding aortic valves are named according to the source of the coronary arteries. Thus, the right and left coronary arteries arise from the right and left aortic sinuses, respectively. The remaining aortic sinus usually lies posteriorly, does not contain a coronary artery and, according to the newest nomenclature, is designated the noncoronary sinus.

The aortic sinuses are intracardiac and cannot be identified on conventional roentgenography. During angiocardiography, they appear as dilatations at the root of the aorta immediately above the aortic valves, and are best visualized in the left anterior oblique view. Inconstant filling of the coronary arteries during angiocardiography does not always allow individual identification of the sinuses. However, in the left anterior oblique view the right coronary sinus is regularly anterior to and just behind the sternum. The aortic sinuses are in close relation to all the cardiac chambers, particularly the right atrium and ventricle. The origin of the pulmonary artery, the interventricular septum and the left atrium are adjacent, whereas the superior vena cava is more distant.

Embryology and Pathology of Congenital Aortic Sinuses: Morgan Jones and Langley [10] have described the embryology of aortic sinus aneurysms. They believe that they arise because of defective development of the distal bulbar septum, which in turn evolves from the bulbus cordis, the primitive exit tube of the heart. Edwards and Burchell [11] have recently reviewed the pathology of aortic sinus aneurysms. They attribute the aneurysm to lack of continuity between the aortic media and aortic ring. In aortic sinus aneurysms, the wall is made up of atrial wall instead of aortic media. The pressure within the aorta causes bulging of the sinus, producing an aneurysm.

The nature of the aneurysmal dilatation of the aortic sinuses in coarctation of the aorta is unknown because histologic study of a case has not been made. In contrast, in Marfan's syndrome Tung and Liebow [12] have shown that medionecrosis of the aorta just above the heart is common, and frequently results in aneurysmal dilatation of the aorta. They report that in that disease the sinuses of Valsalva also become thin-walled and aneurysmal. Normally the elastic fibers of the aortic sinuses are thinner in this area than in the rest of the ascending aorta [13]; with disease they tend to dilate. Even in the absence of autopsy proof it is probable that the aneurysmal dilatation of the aortic sinuses associated with coarctation of the aorta is still another congenital malformation, particularly because multiple congenital malformations associated with coarctation are not uncommon.[14]

Clinical Features: Incidence and Type of Aneurysm: A total of seven aortic sinus aneurysms associated with coarctation of the aorta and one with pseudocoarctation have been diagnosed by angiocardiography. Of these, six were from

TABLE 1

Findings in Five Previously Reported Cases of Aortic Sinus Aneurysm Associated with Coarctation, and One Pseudocoarctation of the Aorta

Case No. and Reference Age Sex Race	Symptoms	Cardiac Murmurs	Blood Pressure, mm. Hg	Electrocardiogram
3. (N.Y.H. No. 632904)[6] 17 M White	Dizziness and headaches	Harsh systolic murmurs all over precordium, transmitted to left axilla and back	Upper, 160/110; lower, 0	Left ventricular hypertrophy
4. (N.Y.H. No. 614924)[6] 18 M Negro	Frequent epistaxis and headaches; hypertension, 2 years	Harsh rough systolic murmur, most marked 2nd right and 4th left interspaces, transmitted to neck	Right arm, 190/130; left arm, 180/110; legs, 0	Early left ventricular hypertrophy
5. (N.Y.H. No. 582445)[6] 20 M White	Asymptomatic, with history of hypertension since childhood	Grade 3 apical systolic murmur and over precordium, radiating to left axilla and neck	Upper, 200/120; lower, 135/120	Normal
6. (N.Y.H. No. 696073)[7] 27 F White	Fever, fatigue, exertional dyspnea, murmur since birth. Bacterial endocarditis age 20 and 26 years	Grade 4 systolic murmur and thrill heard 3rd I.S. right of sternum and precordium, transmitted to the back and abdomen. Also systolic and diastolic murmurs, base of heart. Pulses palpable all extremities	Upper 190/0; lower, 95/40; direct rt. brachial, 227/63 (mean, 122); rt. femoral 110/66 (mean 82), characteristic tracings of coarctation of the aorta and aortic insufficiency	Hypertrophy, left ventricle
7. Goetz and Graham[8] 21 F White	Asymptomatic, with history of cardiac murmur since age 6 years	Prolonged rough systolic murmur at base, transmitted to neck and interscapular area. A softer systolic murmur at apex, with a faint early diastolic murmur at apex transmitted to left axilla. Systolic thrill over base and A_2 increased	Upper, 180/100; lower, 0	Normal
8. (N.Y.H. No. 705228)[6] 26 F White	Backache and heart murmur	Grade 2 systolic murmur over base, loudest left sternum and transmitted to left back and axilla. Loud systolic murmur also heard along course aorta posteriorly and over abdomen	Right arm, 126/96; left arm, 130/90; right leg, 140/120; left leg, 132/110; simultaneous direct pressures of brachial artery, 117/86 (mean, 105), and femoral artery, 119 (mean, 102)	Normal

TABLE 1—(*Continued*)

Case No. and Reference Age Sex Race	Conventional Roentgenogram	Angiocardiogram	Operation, Follow-Up Blood Pressure Readings, Murmurs, Remarks
3. (N.Y.H. No. 632904)[6] 17 M White	Slight rib notching. Enlarged left ventricle, inconspicuous aortic knob	Aneurysmal dilatation aortic sinuses. No dilatation ascending aorta. Coarctation with slight poststenotic dilatation descending aorta. Moderate collaterals	Resection of coarctation with end-to-end anastomosis. Operation uneventful. Two years afterwards, full activity. No complaints. Upper extremities, 120/85; right leg, 130/90; left leg, 148/100
4. (N.Y.H. No. 614924)[6] 18 M Negro	Marked rib notching. Dilated aortic arch and enlarged left ventricle	Aneurysmal dilatation aortic sinuses. Dilated ascending aorta; high arch formed by dilated left subclavian artery and enlarged left ventricle. Coarctation with marked collaterals. Slight poststenotic dilatation of descending aorta	Resection of coarctation with end-to-end anastomosis. After operation, rt. leg. 128/100; left leg, 120/94. Pressures 4 years later; RA, 136/86; RL, 110/90; LL, 118/90. Rough systolic murmur all over precordium, heard best over base, persists. Working, fully active
5. (N.Y.H. No. 582445)[6] 20 M White	Moderate rib notching. Enlarged left ventricle	Moderate dilatation aortic sinuses. Normal ascending aorta. Moderate collaterals. No poststenotic dilatation of descending aorta	Resection of coarctation with end-to-end anastomosis. Postoperative course uneventful. Five years later, full employment and sports. RA, 140/80; LA, 134/76; RL, 156/100; LL, 164/104. Cardiac murmurs persist and unchanged compared to preoperative examination. Working and active
6. (N.Y.H. No. 696073)[7] 27 F White	Moderate rib notching. Enlarged heart, especially left ventricle. Absence aortic knob and indentation of esophagus by descending aorta	Large left ventricle. Dilatation ascending aorta and brachiocephalic vessels. Marked collaterals with coarctation of aorta and saccular aneurysm right aortic sinus, 2.2 cm. in diameter. No poststenotic dilatation of descending aorta	Prior to operation and after antibiotics, developed nocturnal dyspnea; improved after digitalization. Under hypothermia, coarctation resected and end-to-end anastomosis done. Two years later, improved, B.P., 120/40. Murmurs unchanged. Working
7. Goetz and Graham[8] 21 F White	Minimal rib notching and left ventricular enlargement	Coarctation of the aorta, aneurysmal dilatation aortic sinuses. Dilated ascending aorta, no poststenotic dilatation. Moderate collaterals	Excision of coarctation, 3 months later: upper, 128/74; right leg, 110/70; left leg, 130/90. Systolic murmur at apex and base diminished. Early diastolic murmur no longer heard. A_2 less forcible
8. (N.Y.H. No. 705228)[6] 26 F White	Supra-aortic vascular shadow with prominent dilated descending aorta. No rib notching. Esophagram showed inverted figure "3" deformity. Heart not enlarged	Deformed superior vena cava at entrance right atrium with slight filling defect due to aneurysmal dilatation of the aortic sinuses. Ascending aorta dilated (40 mm.). Innominate and left subclavian arteries dilated. An apparent point of coarctation seen below left subclavian artery, with marked poststenotic dilatation of descending aorta. No collaterals	Absence of collateral arterial circulation and the presence of normal blood flow through the aorta *excluded* true coarctation of the aorta. Operation not advised; 3 years later, patient in good health, working and active

The New York Hospital, one (case 2) was from the United States Naval Hospital, St. Albans, N. Y., and the other (case 7) was found in the literature.[5] The true incidence of aortic sinus aneurysm in coarctation of the aorta is difficult to estimate; it occurred six times among 128 patients with coarctation of the aorta studied angiocardiographically at The New York Hospital.

Only one patient (case 6)[7] had involvement of a single aortic sinus. Although the case in the literature (case 7) is reported to have had involvement of the right sinus, the illustrations suggest that there was aneurysmal involvement of all the aortic sinuses.[8] The patient with the right aortic sinus aneurysm (case 6)[7] was also unique in that subacute bacterial endocarditis and frank aortic regurgitation were present. The patient with pseudocoarctation (case 8)[9] had many of the anatomic features of coarctation. However, rib notching was absent, and there were no arterial collaterals or physiologic constriction of the aorta. This case is included in the series because of its resemblance to coarctation; the embryologic development of this anomaly probably is also very similar to that of coarctation.

Age, Sex and Race: The ages of the patients with aortic sinus aneurysms and coarctation of the aorta when first diagnosed by angiocardiography varied from 13 to 27 years, with an average of 21 years. There were five males and three females; only one was Negro (table 1).

Symptoms and Physical Findings: Five patients were asymptomatic at the time of admission, although a history of previous hypertension or heart murmurs was present in every instance (table 1). Three patients (cases 3, 4 and 6) had significant symptoms: headaches were present in two, the third had bacterial endocarditis. Systolic murmurs (grade 3 to 4) transmitted to the axilla and back, especially over the superscapular area and similar to those usually found in coarctation, were common. A diastolic murmur over the aortic area was heard in the patient with bacterial endocarditis and aortic insufficiency (case 6). Another patient (case 7) had a faint early apical diastolic murmur. One patient (case 8) had transmission of a systolic murmur over the back and abdomen along the course of the aorta (table 1).

Hypertension: Elevated upper-extremity blood pressures with diminished-to-absent lower extremity blood pressures were present in every case but one. The latter patient (case 8) (table 1) did not have true coarctation.

Electrocardiography: Left ventricular hypertrophy was present in the electrocardiograms of half the series (cases 1, 3, 4 and 6), and probably represents the effect of hypertension. In the others, although significant hypertension was present in three instances, the electrocardiogram was normal.

Conventional Roentgenography: The chest roentgenogram revealed significant findings in every case. There was enlargement of the heart, especially the left ventricle, in six instances; in two (cases 2 and 8) the heart was normal in size. Deformity of the aortic arches was a common finding. Rib notching was present in all but one patient (case 8). One patient (case 2) had a hypoplastic aortic knob. The patient with pseudocoarctation (case 8) had what appeared to be a dilated aortic arch, but this proved to be a poststenotic dilatation of the descending aorta.

Angiocardiography: The definitive diagnosis of aortic sinus aneurysm is provided by angiocardiography. Aneurysmal dilatation of all of the aortic sinuses was present in all but one case (case 6), and in that, the right aortic sinus alone

was aneurysmal. Left ventricular enlargement varied from a slight to a marked degree. Ascending aortic and brachiocephalic arterial dilatations were common, being absent in only two instances (cases 3 and 5). Of interest is the dilatation of the ascending aorta and brachiocephalic vessels in the pseudocoarctation patient who had normal blood pressures. This suggests that dilatation of the ascending aorta may be part of the malformation and is not always related to hypertension. Two patients with normal size of the ascending aorta (cases 3 and 5) had moderate and severe hypertension. Significant dilatation of collateral arteries (mammary, scapular and intercostal) was present in every case but the one with pseudocoarctation (case 8). Poststenotic dilatation of the descending aorta was marked in the pseudocoarctation patient (case 8) and slight in two instances (cases 3 and 4); in five patients it was absent. Its presence in the pseudocoarctation case with normal blood pressure suggests that the so called poststenotic dilatation may be still another deformity which occurs with coarctation and is probably independent of stenosis.

Diagnosis: The diagnosis of unperforated aortic sinus aneurysms can be made only by contrast visualization of the aortic root.[1, 2] Retrograde aortography established the diagnosis in one instance.[15] Angiocardiography, however, is the preferable method of visualizing the aorta because it avoids arterial puncture. When rupture of an aortic sinus aneurysm occurs, there are often sudden onset of severe dyspnea, chest pain, right heart overloading and evolution of machinery-like murmurs. Confirmation may be made by cardiac catheterization.[16–19]

Coarctation of the aorta should be suspected when there are hypertension and diminished or absent lower extremity pulses or blood pressure. Confirmation may then be had by roentgen studies of the chest which, in adults, frequently shows rib notching, deformity of the arch and enlargement of the left ventricle. Rarely, especially in women, the point of coarctation may be not in the usual site just beyond the aortic arch but in the abdomen. For this reason, but chiefly because the type of coarctation will be visualized and thereby establish the need for a graft, angiocardiography is recommended routinely in coarctation of the aorta.[20] Unless angiocardiography is done, aortic sinus aneurysms associated with coarctation of the aorta will be missed; the surgical exposure for correction of coarctation does not readily permit diagnosis at operation. The tendency of bacterial endocarditis to occur with aortic sinus aneurysms[7, 10] makes diagnosis of more than academic interest. Finally, unusual roentgen findings simulating a mediastinal tumor may occur with pseudocoarctation;[9, 21] differentiation is easily made by angiocardiography.

Treatment: All patients except the one with pseudocoarctation,[9] for whom operation was not indicated, had successful resection of the coarctation and end-to-end anastomosis of the aorta. Follow-up examinations (for as long as five years in one case) have shown a return of blood pressure to normal levels (table 1). In the patient with aortic regurgitation (table 1) the diastolic pressure was 40 mm. Hg. In two instances (cases 1 and 6) hypothermia was used during operation, and it is believed to be especially indicated to prevent undue stress to the aneurysm when clamping of the aorta is done for resection of the coarctation. The presence of an associated aortic sinus aneurysm is a further indication for the surgical treatment of coarctation, because decrease in the hypertension and return of the blood pressure to normal levels may well delay and

even prevent rupture. Finally, after surgery, awareness of the presence of an aortic sinus aneurysm will alert the physician for the need of prophylactic antibiotic therapy when teeth extraction or other minor surgical procedures are necessary.

Prognosis: Although the presence of an unperforated aneurysm of the aortic sinus seems ominous, the prognosis is not necessarily bad. All of the patients in this series of aortic sinus aneurysm and coarctation are working and engaging in sporting activities; rupture has not occurred. One patient (case 6) who had had bacterial endocarditis and was treated has had no recurrence. Furthermore, reduction of hypertension by correction of the coarctation of the aorta promises to be beneficial by reducing stress and tendency of the aortic sinus aneurysm to rupture.

Summary

Two new patients with aneurysmal dilatation of the aortic sinuses (of Valsalva) and coarctation of the aorta are compared with six previously reported cases. It appears that while coarctation of the aorta can readily be recognized clinically and roentgenographically, the diagnosis of the aortic sinus aneurysm is subtler and requires contrast study of the aorta, especially angiocardiography.

Knowledge of the presence of aortic sinus aneurysm associated with coarctation is important because it will alert the surgeon to the need for hypothermia during surgical resection of the lesion, and will thereby avoid undue stress. Subsequently, knowledge of the presence of the congenital aortic sinus aneurysm will also establish the need for the prophylactic use of antibiotics when teeth extractions and other minor surgical procedures are contemplated. The prognosis of aneurysms of the aortic sinus and coarctation of the aorta need not be serious. Postoperative follow-up examinations (as long as five years in one patient) have revealed that the unruptured aortic sinus is unusually well tolerated and is compatible with regular work and sporting activities.

Addendum

Since this paper was submitted for publication, another patient with aneurysmal dilatation of the aortic sinuses and coarctation of the aorta has been studied. A 44 year old Negro had had a history of hypertension of 15 years' duration and had developed dyspnea and cough during the last year. Physical examination disclosed hypertension (200/110 mm. Hg) in the arms with 140 mm. Hg systolic blood pressures in the legs. A systolic (grade 3) murmur was heard over the entire precordium. Rib notching, marked ventricular enlargement and dilatation of the ascending aorta were present in the roentgenogram of the chest. Angiocardiography on December 5, 1957 disclosed the aneurysmal dilatation of the aorta to extend into and include the aortic sinuses. A 2×3 cm. aneurysm of an intercostal artery near the point of coarctation was also recognized. At operation, advanced arteriosclerosis of the thoracic aorta was found and the aneurysmally dilated ascending aorta and intercostal artery aneurysm appeared too friable to attempt excision of the coarctation and reanastomosis of the aorta. When last seen on August 19, 1958, the patient was still dyspneic and the blood pressure of the arms was 200/132 mm. Hg.

Summario in Interlingua

Es reportate duo casos additional de aneursyma de sino aortic (de Valsalva), associate con coarctation del aorta. Le casos es comparate con sex alteres de publication anterior. Apparentemente, durante que coarctation es facile a recognoscer super le base de observationes clinic e roentgenographic, le diagnose de aneurysma

de sino aortic es plus subtile e require un studio del aorta con le uso de substantia de contrasto.

Le correction chirurgic del coarctation es specialmente importante proque illo resulta in un reduction del hypertension e del stress in le aneurysma. Le information que un aneurysma de sino aortic es presente signala al chirurgo le necessitate del uso de hypothermia durante le resection aortic pro prevenir un augmento del stress in le aneurysma. Postea—viste le tendentia del contraction de infectiones bacterial in le presentia de aneurysma de sino aortic—il es desirabile provider un prophylaxe antibiotic in le extraction de dentes e le effectuation de altere minor interventiones chirurgic.

Le prognose in casos de aneurysma de sino aortic non pare esser serie. Examines post-operatori (durante periodos de usque a cinque annos in un del patientes) ha revelate que labor regular e activitate sportive es ben tolerate. Ruptura de aneurysma non ha occurrite in iste serie.

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THROMBOTIC THROMBOCYTOPENIC PURPURA: REPORT OF A CASE AND REVIEW OF THE LITERATURE *

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Thrombotic thrombocytopenic purpura is an uncommon condition characterized by thrombocytopenia, hemolytic anemia and widespread occlusions of arterioles and capillaries. The vascular occlusions affect the central nervous system to a particularly great degree, producing diverse neurologic signs and symptoms. The earliest report of this disease was by Moschcowitz in 1925 under the title, "An Acute Febrile Pleochromic Anemia with Hyaline Thrombosis of the Terminal Arterioles and Capillaries." [1] Several other descriptive terms were employed until 1947, when "thrombotic thrombocytopenic purpura" was proposed by Singer et al.[2] Although this designation fails to emphasize the hemolytic factor, it is the term most commonly used in the literature. Up to the present time, about 60 cases of thrombotic thrombocytopenic purpura have been reported, the majority since 1950. With few exceptions, the diagnosis has been made post mortem.

The following case report illustrates the clinical and laboratory findings which permitted the antemortem diagnosis of thrombotic thrombocytopenic purpura, with subsequent pathologic confirmation.

Case Report

A 33 year old Greek woman was seen in consultation because of headache and dizziness. The first indication of illness had occurred one month previously, with sudden vertigo and momentary loss of consciousness. Thereafter, she was beset by frequently recurring vertigo, tinnitus, and two additional episodes of syncope, once while descending a flight of stairs. During the two weeks prior to examination she had been forced to stop working as a waitress because of extreme generalized weakness. Vomiting had been present for two days. The past history was unremarkable except for the delivery of quadruplets at age 20; only one of the infants

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survived. Medication taken since the beginning of the present illness was limited to aspirin.

Examination disclosed an acutely ill woman who was barely able to sit up, and was unable to walk without support because of dizziness and weakness. The skin and mucous membranes, including the palmar creases, were markedly pale. Unusual chamois-colored patches were present on the upper abdomen and the dorsa of both feet.

The temperature was normal; pulse rate, 100° F.; blood pressure, 100/70 mm. of Hg. Funduscopic examination was negative. The pupils were equal and showed normal reflexes. External ocular movements were normal, and nystagmus was not

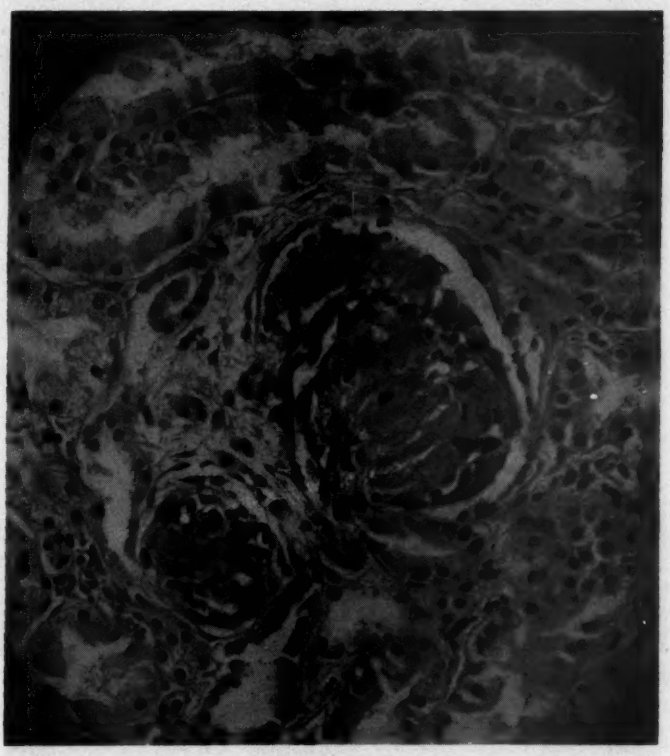

FIG. 1. Kidney section showing two hyaline thrombi with early organization. 280×.

noted. The ears, nose and throat were normal. The heart and lungs were not remarkable. The liver and spleen were not palpable. Pelvic examination revealed slight enlargement and irregularity of the uterus. Neurologic examination was negative except for inability to elicit the abdominal skin reflexes. There was no lymphadenopathy.

Urinalysis showed a trace of albumin and a moderate number of leukocytes. The hemoglobin was 6.6 gm.; erythrocyte count, 2.25 million; hematocrit, 21%. The leukocyte count was 5,750, with a normal differential count. The platelets numbered 44,000. Reticulocytes, 11.6%. Target cells were noted on peripheral

blood smears. Samples of sternal marrow obtained by aspiration showed acceleration of erythrogenesis. Megakaryocytes were present in adequate numbers, but there was little evidence of platelet formation.

Stool examinations for occult blood were negative initially. The direct bilirubin was negative; the indirect, 0.47 mg.%, later rising to 0.84 mg.%. Determinations of blood sugar and blood urea nitrogen were within normal range. The serologic test for syphilis was negative. Roentgenograms of the chest and skull demonstrated normal findings. An electrocardiogram showed sinus tachycardia and depression of ST segments in V 2, 3, 4 and 5.

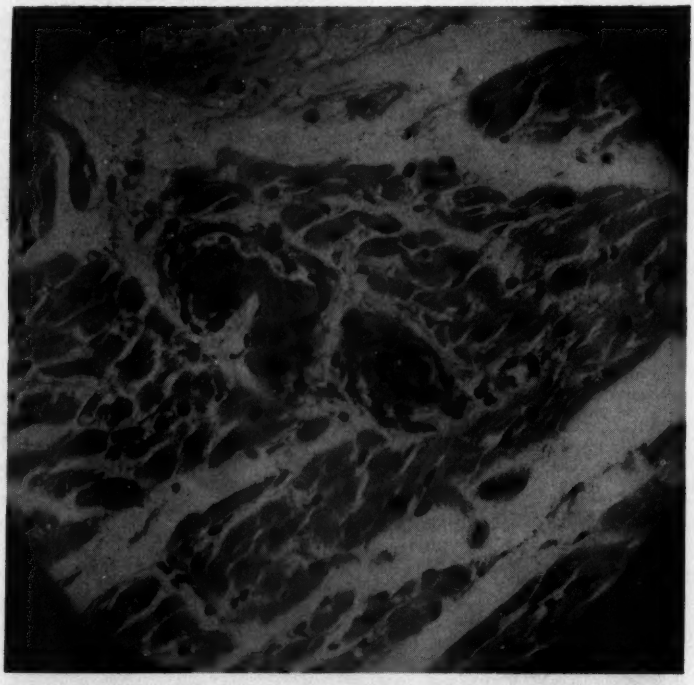

FIG. 2. Section of myocardium demonstrating two intrinsic thrombi in an early stage of development. 280 ×.

The Lee-White coagulation time varied from nine and one-half to 14 minutes. Clot retraction on several occasions was incomplete after 48 hours. The initial bleeding time was 26 minutes. The prothrombin time was 14.4 seconds, with a control of 13.4 seconds. The Coombs' test was negative. An osmotic fragility test showed beginning hemolysis in 0.48% saline, complete hemolysis in 0.28% saline. The mechanical fragility in O_2 was 11%; in CO_2, 15.6%. No circulating agglutinins or hemolysins were present at 4°, 27° or 37° C. The hemolytic index was 27.1.

Five hundred cubic centimeters of whole blood were administered daily for five days, following which the hemoglobin was 9.3 gm., erythrocytes, 2.81 million, and platelets, 8,000. Vaginal bleeding began on the second hospital day and persisted. A positive Rumpel-Leede test was present on the second day, and purpura appeared

on the fourth day. The bleeding time was 38 minutes. Free oozing occurred at the sternal puncture site and wherever needles were inserted.

Cortisone was started in a daily dose of 300 mg. orally on the fourth day, with gradual reduction to 100 mg. daily. On the sixth day of cortisone the bleeding time was reported at 11.5 minutes, although the platelet count was 10,000. At this time confusion and slurred speech were noted, and examination revealed left hemiparesis. The following day these abnormalities had entirely disappeared and the patient was mentally clear. The diagnosis of thrombotic thrombocytopenic purpura seemed reasonably certain, and splenectomy was contemplated, but before this could be accomplished convulsions appeared. The first several seizures were entirely left-sided, but subsequently became generalized, followed by coma. On the thirteenth day the laboratory reported the hemoglobin to be 10.2 gm.; red blood cells, 3.16 million; platelets, 166,000; bleeding time four and one-half minutes. Fever was present for the first time and persisted, reaching 106° F. prior to death. Seizures occurred with increasing frequency until death on the fifteenth day after admission.

Autopsy Findings: Aside from scattered purpuric lesions, the external surface of the body was not remarkable. The pleural surfaces of both lungs appeared hemorrhagic, and the cut surface of both lower lobes was hyperemic. The pericardial cavity contained 100 c.c. of bloody fluid. The heart weighed 340 gm. The epicardial surface was dotted by small petechial hemorrhages; these lesions were also present within the myocardium and on the endocardial surface. Examination of the stomach and intestines revealed no abnormalities. The liver weighed 1725 gm. and the spleen 240 gm.; both organs were hyperemic. The genitourinary tract, pancreas and adrenals showed no gross abnormalities.

Microscopic examination revealed widespread occlusions of arterioles and capillaries involving principally the brain and heart, with less marked but definite involvement of pancreas, kidneys and adrenals (figures 1 and 2). There was endothelial proliferation of varying degree, suggesting variation in age of the lesions.

The pathologic diagnosis was thrombotic thrombocytopenic purpura with lesions present in the lungs, heart, kidneys, adrenal glands, pancreas and brain.

Discussion

The etiology of thrombotic thrombocytopenic purpura remains obscure; however, evidence that the disease is related to the "collagen diseases" is slowly accumulating. The original theory—that the vascular occlusions were due to agglutination of platelets, thereby reducing the number of circulating platelets, and that the erythrocytes were lost into the connective tissues and destroyed—has been largely abandoned. A prime obstacle in clarifying the problem is the failure of platelets to stain specifically. Gore [3] was the first to emphasize the presence of focal vascular lesions of capillaries and arterioles, with swelling and endothelial rupture leading to conglomerations of platelets. Because of the variation of the lesions, Gore proposed their development in "showers." Meacham [4] and Orbison [5] both took issue with the platelet theory, stating that thrombotic thrombocytopenic purpura is in actuality a diffuse vascular or collagen disease. March [6] has presented evidence that the vascular occlusions are initiated by endothelial swelling, with later appearance of a bland thrombus. Adelson, Heitzman and Fennessey [7] found a markedly shortened survival time of transfused platelets and erythrocytes, but were unable to demonstrate abnormal hemolysins or agglutinins.

Several authors have pointed out superficial similarities between lupus erythematosus, polyarteritis nodosa and thrombotic thrombocytopenic purpura,

suggesting that the three diseases are related; however, present evidence is too meager to bear this out.[8, 9, 10] Recently, Lazlo [11] reported the case of a young woman who died of lupus erythematosus, with the postmortem finding of platelet thrombi considered to be typical of thrombotic thrombocytopenic purpura. The possible role of hypersensitivity is suggested by Gendel's [12] two patients, both of whom had exhibited reactions to penicillin, and by Barondess.[13]

The diagnosis of thrombotic thrombocytopenic purpura is not difficult if the typical features are present and recognized. The disease occurs more frequently in relatively young females, but has been found in both sexes from the first to the seventh decade. Wile [14] has reported three cases in children from 10 months to eight years of age. Upper respiratory infection is a frequent precursor. Headaches, malaise, fatigability and dizziness, and nausea and vomiting are common premonitory symptoms. Not infrequently the patient is seen only when hemorrhagic manifestations have made their appearance.

Pallor is a striking and early manifestation, often preceding obvious signs of bleeding. A patchy brownish discoloration of the skin may be present.[15] Jaundice is never marked, but hyperbilirubinemia may be found by laboratory methods. Purpura soon appears, together with hematuria and gastrointestinal and vaginal bleeding. The tourniquet test is invariably positive. Hepatosplenomegaly has been present in about one-half of the reported cases. Of the cases reviewed, only one was afebrile; [16] however, fever may not develop until the preterminal stage of the disease.

Signs of central nervous system involvement are outstanding. These vary from restlessness and confusion, slurred speech and aphasia to delirium, convulsions, hemiplegia and coma. The neurologic manifestations often disappear quickly in the initial stages, but become more pronounced as the disease progresses. The cerebrospinal fluid rarely shows more than a slightly elevated protein content and perhaps a few red blood cells; evidence of frank cerebral hemorrhage, such as commonly occurs in idiopathic thrombocytopenic purpura, is lacking.

The anemia, which may be mild early in the course of the disease, is normocytic-normochromic in type. The invariable reticulocytosis prompts a search for hemolysis which can be verified by an increased urinary and fecal urobilinogen output and by an elevation of indirect-reacting serum bilirubin. The daily output of fecal urobilinogen may be only slightly increased above normal; it is therefore necessary to correlate this determination with the circulating hemoglobin (hemolytic index). The Coombs' test is invariably negative.

The reactions of the erythrocytes in thrombotic thrombocytopenic purpura to the various fragility tests follow no characteristic pattern. Singer [17] has observed intermittent spherocytosis, and states that increased fragility may be demonstrated only after repeated testing. In the majority of reported cases the platelet counts have been 100,000 or less. The thrombocytopenia may be intermittent; therefore, normal platelet counts have been observed at times. Wide variations in leukocyte counts have been recorded—from normal to over 50,000—and leukemoid reactions have been a rather common finding. Prolonged bleeding time and poor clot retraction are always present. Bone marrow studies invariably disclose accelerated erythrogenesis, a reflection of the hemolytic anemia. Some observers have reported normal numbers of megakaryocytes, while others

have noted increased numbers of megakaryocytes together with decreased platelet formation, findings commonly observed in idiopathic thrombocytopenic purpura.

As stated, the diagnosis of thrombotic thrombocytopenic purpura is relatively easy provided the triad of thrombocytopenia, hemolytic anemia and bizarre neurologic manifestations is present and its significance is appreciated by the clinician. Thrombotic thrombocytopenic purpura should be considered in every case of thrombocytopenic purpura. While both hemolytic anemia and thrombocytopenia may develop concurrently in other diseases, the rapidly changing central nervous system signs are seen only in thrombotic thrombocytopenic purpura. In one instance, skin biopsy provided the diagnosis.[8] Cooper [18] was able to demonstrate the typical vascular lesions in bone marrow in two cases.

Although thrombotic thrombocytopenic purpura is generally fatal within a period of days to weeks, Meacham [4] has reported survival for two years after splenectomy, while Gardner's [19] patient lived nine months following splenectomy. In several other cases, splenectomy has not influenced the fatal progression of the disease. Recurrent episodes of purpura over a six-year period, with death due to thrombotic thrombocytopenic purpura, has recently been reported.[16] Possibly mild, nonfatal forms of the disease exist.[20]

ACTH and cortisone have produced seemingly beneficial effects, but these have been transient; certainly the response falls far short of that occurring in idiopathic thrombocytopenic purpura and other types of hemolytic anemia. Transfusions of whole blood and platelets are disappointing, due to the rapidity with which transfused cells are destroyed. Anticoagulants have been suggested, on the theory that the vascular occlusions would be reduced; in practice this has not proved to be the case. Large doses of sulfonamides and antibiotics have been unavailing.

The clinical and laboratory features of the case under discussion were sufficiently typical to permit a presumptive diagnosis of thrombotic thrombocytopenic purpura after seven days of observation. While little beneficial effect resulted from transfusion of whole blood, the administration of cortisone did appear to produce temporary improvement. Nevertheless, the disease terminated fatally while splenectomy was being contemplated. Unilateral convulsions were a prominent feature.

Although no definite conclusions can be reached concerning the cause of thrombotic thrombocytopenic purpura, it is probable that it is primarily a diffuse vascular disease resulting from abnormal immunologic mechanisms, the nature of which remains obscure. Since no method of therapy has proved of great value in thrombotic thrombocytopenic purpura, it is suggested that cortisone be given as soon as the diagnosis is reasonably established, and that splenectomy be carried out with as little delay as possible, regardless of the risk of subjecting a critically ill patient to surgery. Such a course of procedure may prolong life in an otherwise universally fatal situation.

Summary

Thrombotic thrombocytopenic purpura is a disease of unknown etiology characterized by thrombocytopenia, hemolytic anemia and bizarre neurologic manifestations. The diagnosis is not difficult if the typical clinical picture is recognized. An illustrative case is described and the recent literature on the subject reviewed.

It is suggested that earlier diagnosis, administration of cortisone or related steroids, and splenectomy may forestall the usual rapidly fatal progression of the disease.

Summario in Interlingua

Thrombotic purpura thrombocytopenic es characterisate per thrombocytopenia, anemia hemolytic, e extense occlusiones de arteriolas e capillares. Le systema nervose central es extensemente interessate per le lesiones vascular que produce un grande varietate de manifestationes neurologic. Le etiologia de thrombotic purpura thrombocytopenic es incognoscite. Tamen, indicationes que il se tracta de un processo affin al "morbos de collageno" deveni de plus in plus numerose. Un del conclusiones del studio del problema es que le occlusiones vascular es initiate per un tumescentia endothelial, con le formation subsequente de un thrombo blande.

Le morbo occurre le plus frequentemente in feminas de relativemente juvene etates. Mal de capite, vertigine, e nausea e vomito es commun symptomas premonitori. Purpura se manifesta tosto, insimul con hematuria e sanguination gastrointestinal e vaginal. Febre es un constatation constante, sed il pote occurrer que illo se presenta solmente a stadios tardive del morbo. Le manifestationes del systema nervose central include confusion, paralyse, convulsiones, e coma. In le stadios precoce, le signos neurologic pote resolver se e recurrer con rapiditate extraordinari. Anemia normocytic-normochromic e reticulocytosis es constatationes constante. Determinationes de bilirubina seral, urobilinogeno urinari e fecal, e le indice hemolytic confirma le presentia de anemia hemolytic. Thrombocytopenia, prolongation del tempore de sanguination, e imperfecte retraction del coagulo es constatate in omne casos. Le varie tests del fragilitate non exhibi characteristicas constante o de valor diagnostic. Le lesiones vascular ha essite trovate in sectiones de medulla ossee, sed le diagnose definitive depende primarimente del recognition del frappante tableau clinic. Le differentiation ab altere statos hemolytic e thrombocytopenic es importante, proque thrombotic purpura thrombocytopenic es mortal sin exception. In casos isolate, splenectomia ha apparentemente resultate in un relentation del progresso del morbo. ACTH e cortisona ha producite solmente leve grados de effecto benefic. Tamen, iste drogas debe esser usate le plus promptemente possibile, in le spero que splenectomia pote esser effectuate a bon successo.

Es presentate un caso illustrative in que le diagnose de thrombotic purpura thrombocytopenic esseva establite ante morte e confirmate al necropsia.

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GAUCHER'S DISEASE IN IDENTICAL TWINS *

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Gaucher's disease is a rare familial disorder characterized by a disturbance of cerebroside metabolism with abnormal storage or retention of kerasin in the cells of the reticuloendothelial system. The classic clinical findings are splenomegaly, pingueculae, symmetric pigmentation, moderate anemia with leukopenia, "Erlenmeyer flask" deformity of the distal humerus, and a good state of physical preservation. The diagnosis is established by finding Gaucher's cells in the bone marrow aspirate. The entity was first described in 1882 by Gaucher,[1] who considered it a primary epithelioma of the spleen. By 1955, 280 cases had been reported in the literature.[2] Since Gaucher's original description of the disease, many excellent reviews dealing with this subject have been written.[3–10] It is not

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the intent of the authors to enlarge on these clinical or pathophysiologic descriptions.

The hereditary and familial background of Gaucher's disease attracted the attention of investigators as early as 1895, when Collier [11] reported the first case of a familial nature involving a six year old child whose older sister had died of a fatal splenic enlargement. Five years later Bovaird [12] reported two cases involving sisters in a family of 10 children. The following year three cases in one family were reported by Brill.[13] Further reports in 1909 by Brill, Mandlebaum and Libman [14] involved the second of four cases occurring in a single generation of a family previously reported. By 1913 Brill and Mandlebaum [15] found that seven familial cases had been reported. They felt that there appeared to be no tendency for hereditary transmission, since in none of the established cases had any parent been afflicted. Santee [16] in 1927 added two more cases involving brothers.

Hoffman and Mackler [4] in 1929 reviewed 89 cases reported in the world literature and found that there was a familial history in one third of the cases, and that 16% of the cases were one year of age or under. The youngest reported case [17] was an infant who had clinical signs of the disease at one week of age and who died when a year old. They felt that the disease was undoubtedly congenital in addition to being familial, although they had found no parents of children with Gaucher's disease to be suffering from the disease, nor any case of transmission from an adult to a child. Reich et al.[10] in their review in 1951 likewise estimated that about one third of the reported 250 cases had a familial history. In their own series of 20 cases they found both sexes about equally affected, and 95% to be in patients of Jewish extraction.

Groen [18] in 1949 reviewed 64 previously reported cases occurring in 25 families, and added 25 more cases occurring in six additional families. In 23 families of the 25 reviewed in the literature there was horizontal spread only, in that the disease was present in members of one generation with involvement of brothers and sisters or cousins. In no instance were parents or grandparents of patients, or offspring of patients, found to have the disease. In two of their reported families, however, there was a vertical occurrence. A father and two sons and a father and two daughters were found to be afflicted. Groen [18] hypothesized that the hereditary mechanism was based upon a mutation which, once established, was transmitted as a simple dominant hereditary trait. In the affected individuals this trait gave rise to a disturbance of lipid metabolism which resulted in the accumulation of kerasin in the reticulum cells throughout the body. In the family trees presented it appeared that the disease tended to become more severe in each succeeding generation until, after two to three generations, it became clinically manifest early in life in those affected. In the next generation the disorder established during fetal life would culminate in abortion, stillbirth or early death of the affected infant. In this way the mutation extinguished itself by permitting only those unaffected offspring of affected individuals to survive. Reich et al.[10] felt that evidence was not completely convincing for this view.

Reports of multiple-generation occurrence have been infrequent. Anderson [19] in 1933 cited two proved cases in daughters, one confirmed by splenectomy and the other by splenic biopsy. Another daughter was found to have splenomegaly, but further investigation was not permitted. Three sons and both

parents were found to be clinically normal. A paternal grandmother was noted to have an enlarged abdomen and a yellowish brown discoloration of the skin. Pathologic confirmation, however, was not obtained. The author postulated that hereditary transmission was probable and that the mechanism was a passage through a male to the female. It was only recently (1949) that vertical passage was actually proved by Groen,[18] who cited his two cases. The father with the two daughters afflicted with Gaucher's disease was asymptomatic and was found to be a subclinical case only by demonstration of Gaucher's cells in his bone marrow. Stransky and Dauis-Lawas [20] in 1949 reported two cases of children with verified acute Gaucher's disease and one probable, all in one family. The first patient died at 14 months and the second was still alive at 13 months. The father appeared clinically normal, but the authors were able to detect Gaucher's cells in the bone marrow of the mother. This was probably the first report of the infantile type of Gaucher's disease in which the "carrier" could be detected. Stransky and Conchur [21] reported similar instances two years later when they found a 20 months old female infant with Gaucher's disease whose father had Gaucher's cells in his bone marrow without any clinical symptoms, and also in an apparently healthy mother of another infant similarly affected. Geddes and Moore [22] likewise felt that such reported findings indicate that the pathologic genes may be present in the "carrier" state. These investigations confirmed Groen's [18] earlier statement that sternal marrow examinations are indicated in every genetic investigation of Gaucher's disease as the best method presently available to detect such subclinical cases.

Herndon and Bender [23] elucidated further on the hereditary mechanism of the disease when they cited five cases in Negroes involving five separate but closely related sibships, with parents of four of the affected children being second cousins. They pointed out that this occurrence of multiple-cousin marriages would be highly effective in bringing a rare recessive gene into the homozygous state. Utilizing the analysis—coefficient of inbreeding, they concluded that Gaucher's disease was due to the action of an autosomal recessive gene which, in the homozygous state, produced the intracellular metabolic defect resulting in a deposit of kerasin in the reticuloendothelial cells.

In view of the familial background of many of the histories of patients with this disorder, it was felt that the following two cases of Gaucher's disease in identical twins would be of interest. One of the twins (case 2) has been reported by Decker and McWhorter.[24] It is interesting to note that this patient knew that her twin sister had a large spleen but did not know the nature of her disorder. It was our good fortune to have the other twin sister enter our hospital recently, at which time she was unaware of her diagnosis. As far as we can determine, this is the first reported instance of this disease in identical twins.

Case Reports

Case 1. A 32 year old white female was admitted to the hospital on April 23, 1956, for medical observation of hepatosplenomegaly. She had been apparently well until three years prior to this admission, when she noted a pulling, tugging sensation in the left upper quadrant with occasional twinges of sharp, nonradiating pain. Over the intervening years she had noted a gradual fullness in the left upper quadrant and a palpable mass. She did not, however, avail herself of medical attention. In February, 1956, because of spotting on two occasions, she consulted a gynecologist.

The previous normal menstrual period was January 1, 1956. In February, 1956, she had noted the subjective symptoms of pregnancy. The physician's impression was intra-uterine pregnancy, and during the course of his abdominal examination splenomegaly was noted. A hematologic examination, presumably normal, had been done seven years prior to this admission, during hospitalization for an apparently uneventful delivery. The patient stated that she had noted irregular epistaxis and easy bruising throughout her entire life, with no recent aggravation. She denied gall-bladder disease or symptoms thereof, lymph node enlargement, palpitation, malaise or change in the color of her skin.

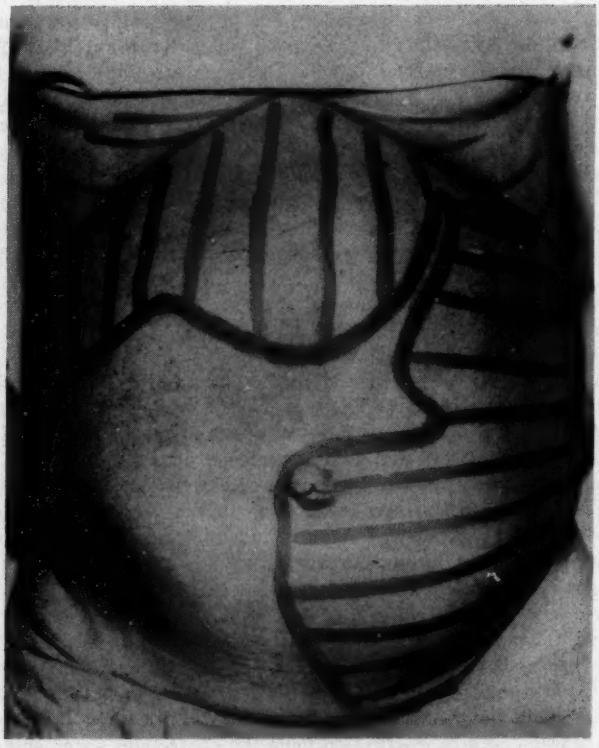

FIG. 1. *Case 1.* Patient's abdomen, showing the extent of enlargement of liver and spleen.

Past and Family History: An identical twin had undergone splenectomy on April 18, 1947, early in the course of her pregnancy. Investigation revealed that the pathologic diagnosis was Gaucher's disease.

Physical Examination: The patient was a well developed, well nourished white female who did not look acutely or chronically ill. The vital signs were as follows: height, 5 feet; weight, 104 pounds; temperature, 98.6° F.; pulse, 80; blood pressure, 104/62 mm. of Hg. The skin was moderately pale but not icteric. The venous pattern over the breasts was increased, with engorgement of the ductal system. Cardiorespiratory system was normal. Bilateral, wedge-shaped, brownish yellow lesions

were noted at the medial aspect of the corneoscleral junction. The left hemidiaphragm was elevated two interspaces, with one half interspace excursion on deep inspiration. The abdomen was full, most markedly on the left. The liver was palpable four fingerbreadths below the right costal margin, with the right and left lobes easily discernible. There was minimal tenderness. The spleen was markedly enlarged, extending to two fingerbreadths above the pubic symphysis. The notch at the splenic hilum was easily palpable. There was no abdominal venous pattern or ascites, and no remarkable lymphadenopathy was noted. Brownish discoloration of the skin was absent.

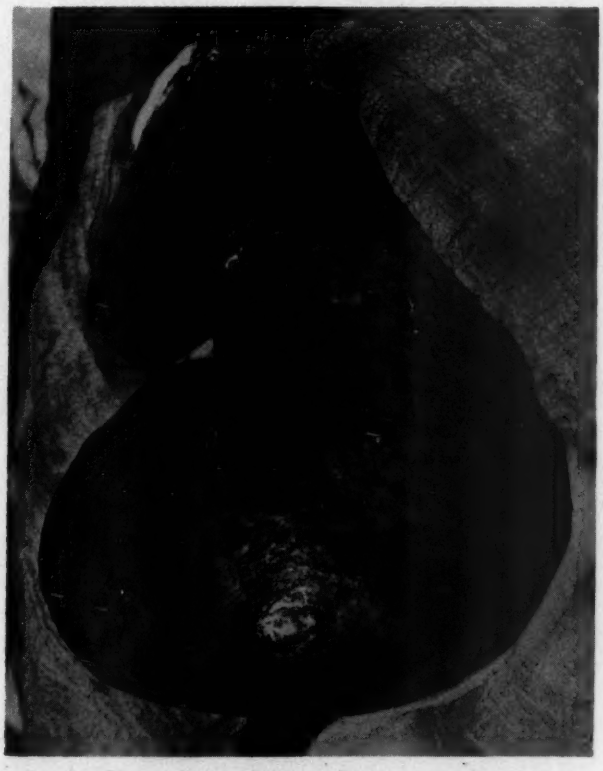

FIG. 2. *Case 1.* Enlarged liver and spleen exposed at surgery.

Laboratory Data: On April 13, 1956, the white blood count was 4,000 per cubic millimeter, with 71% neutrophils, 1% band forms, 28% lymphocytes and 1% monocytes. The red blood count was 3,000,000 per cubic millimeter, with hemoglobin, 9.8 gm.%; hematocrit, 29%; platelets, 52,000 per cubic millimeter. The MCV was 99; MCH, 33; MCHC, 33; reticulocytes, 0.2 per cubic millimeter. The bleeding time was 2 minutes; clotting time, 3¾ minutes. After four transfusions of 500 c.c. of whole blood the white blood count was 12,150, with 93% neutrophils, 8% band forms, 4% lymphocytes and 3% monocytes. The red blood count was 3,980,000, with 15.5 gm.% hemoglobin and 47% hematocrit. The cardiolipin complement

fixation and urinalysis were negative. The plasma prothrombin time was 96%. The serum prothrombin time was 36%, with a prothrombin consumption of 51%. Both sternal bone marrow aspirations demonstrated typical Gaucher's cells. The liver function tests were normal. Chest film revealed a small fibrocalcific density, interpreted as a residual of old inflammatory disease in the left midlung field. The left diaphragm was high in position, with the basilar portions of both lung fields revealing slight exaggeration of bronchovascular markings. The femoral x-rays were normal. The patient was operated upon on May 7, 1956. On May 14 the white

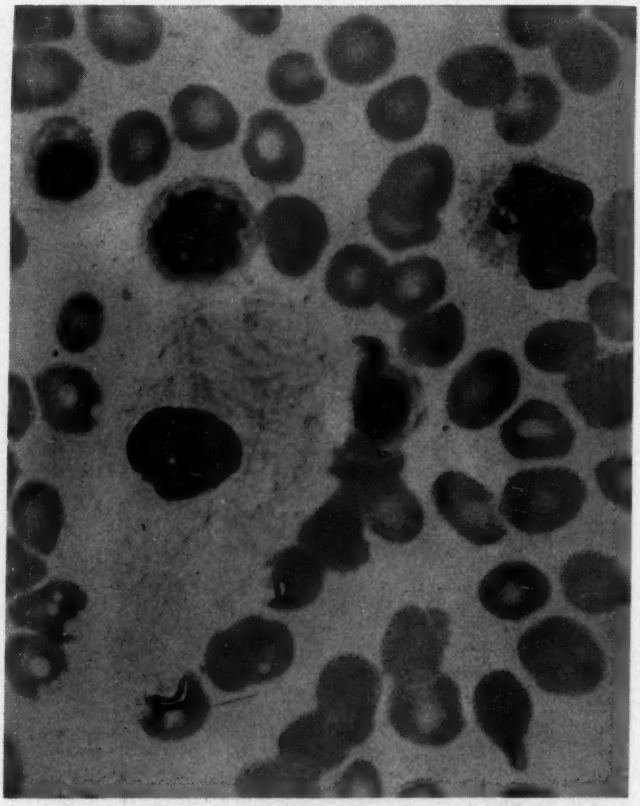

FIG. 3. *Case 1.* Gaucher's cell in bone marrow aspirate. (× 900.)

blood count was 7,200, with 72% neutrophils, 2% band forms, 25% lymphocytes, 2% monocytes and 1% basophils. The red blood count was 3,650,000, with a hemoglobin of 14.7 gm.%, 448,000 platelets, a sedimentation rate of 26 millimeters and a hematocrit of 46%.

Course in Hospital: The patient presented a problem of massive splenomegaly with hepatomegaly and a moderate normochromic, normocytic anemia. Both bone marrow aspirations revealed the typical cells of Gaucher's disease. Surgical and obstetric consultants concurred in the opinion that splenectomy was indicated because

of the massive spleen, which had recently become symptomatic and which might interfere with normal gestation and delivery. The patient was prepared with 1,000 c.c. of whole blood. On May 7, 1956, splenectomy was performed and a huge spleen delivered without difficulty. During the course of abdominal exploration the gallbladder was found to contain numerous faceted calculi, and cholecystectomy was therefore performed immediately after the splenectomy. The patient received 1,000 c.c. of whole blood during surgery. The postoperative course was uneventful, and

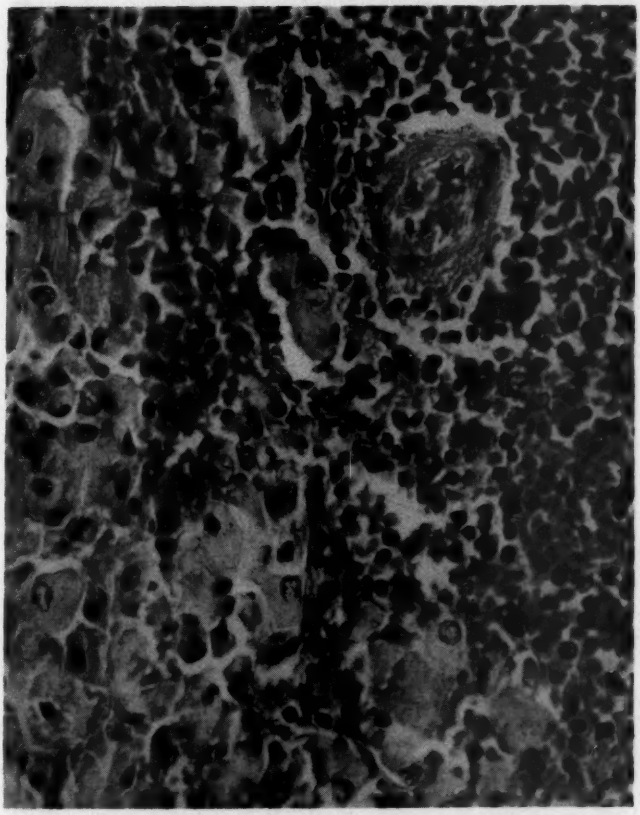

FIG. 4. *Case 1.* Section of spleen showing numerous clusters of Gaucher's cells. (× 475.)

the drain was removed on May 11, 1956, with sutures being removed on May 14, 1956. On June 8, 1956, the platelets were 428,000, with hemoglobin, 12.2 gm.%; white blood count, 18,650, with 80% neutrophils, 13% lymphocytes, 4% monocytes and 3% eosinophils. On August 1, 1956, the platelets were noted to be 114,000; white blood count, 11,900, with 71% neutrophils, 20% lymphocytes, 8% monocytes and 1% eosinophils. This last report was in the sixth month of pregnancy. On October 9, 1956, the patient delivered a seven pound, three ounce male without difficulty and at present (January, 1957) both mother and child are asymptomatic.

Pathologic Examination: *

Gross: Examination of the spleen revealed it to be markedly enlarged and firm, weighing 2,535 gm. and measuring 33 by 17 by 7.5 cm. The cut surface bulged slightly and oozed liquid blood. It was a light red-brown, and the pulp would not scrape off on the back of a knife. Careful examination of the surface revealed numerous faintly visible, slightly glistening 0.5 to 1 mm. nodules. A needle biopsy of the liver was not grossly remarkable. The gall-bladder was slightly distended,

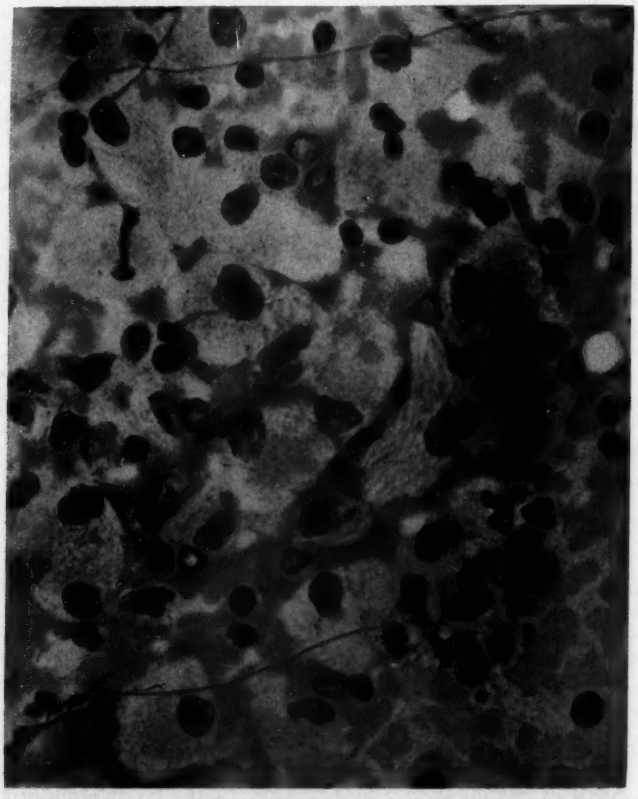

FIG. 5. *Case 1.* Numerous Gaucher's cells in splenic imprint. (× 475.)

had a moderately thickened wall, and contained 49 faceted mixed stones, averaging approximately 0.7 cm. in diameter.

Microscopic: Microscopic sections of both the spleen and the liver showed the parenchyma to be infiltrated with numerous large histiocytic cells, with increased amounts of cytoplasm showing fibrillary striations. Bone marrow aspiration had previously shown a few similar cells. The sections of the gall-bladder demonstrated moderate fibrosis and chronic inflammation of the wall but no similar histiocytic cells.

* Detailed pathology by Captain Robert S. Cox, Jr., Pathology Service, Letterman Army Hospital, San Francisco, California.

Diagnosis: Gaucher's disease, involving spleen and liver, severe. Cholecystitis and cholelithiasis.

Case 2. A 26 year old white female was first admitted to a U. S. Air Force Hospital on October 18, 1950, for investigation of anemia and splenomegaly. Her only complaints at that time were fatigue, palpitation and lightheaded attacks of three months' duration. She denied any history of jaundice, clay-colored stools or dark urine. Her menses were slightly irregular, with occasional excessive flow. Her

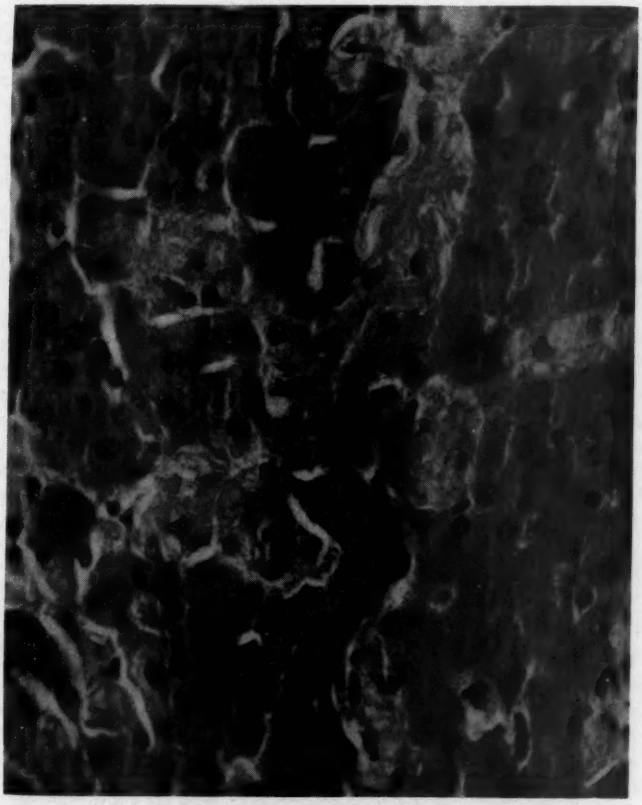

FIG. 6. *Case 1.* Liver biopsy showing numerous clusters of Gaucher's cells. (× 475.)

last period was three months overdue, and she was examined in the outpatient department prior to hospitalization and found to have signs suggestive of pregnancy.

Past History: In July, 1947, she had undergone cholecystectomy for right upper quadrant pain in a civilian institution. Operative summary revealed chronic cholecystitis with cholelithiasis. At surgery the spleen was enlarged to two and one-half times the normal size, with no evidence of perisplenitis. The liver appeared slightly enlarged, with yellowish mottling. A biopsy was taken which revealed "cirrhosis, early, slight." The patient made an uneventful recovery. Serial liver function tests done subsequently were found to be normal.

She was next seen by a physician in October, 1949, for her first pregnancy. At this time it was noted that her liver and spleen were still enlarged. Her pregnancy was uneventful except for premature labor, and she delivered a normal, six pound, 11 ounce infant on December 30, 1949, approximately five weeks before her estimated date of confinement. Three months later she was hospitalized for observation because of acute lower abdominal pain diagnosed as a ruptured graafian follicle cyst. On palpation the liver was thought to be smaller than had previously been reported, and the spleen was found to extend to the level of the umbilicus on deep inspiration. Blood count at this time revealed a mild normochromic, normocytic anemia, with a white blood count of 4,450 per cubic millimeter and an essentially normal differential. Her mother stated that "liver weakness" ran in the family, although there was no history of known jaundice. The patient's identical twin sister, who has one child, was known to have moderate anemia and splenomegaly.

Physical Examination: Examination revealed a 26 year old sallow white female with bilateral yellowish conjunctival pingueculae and a freckled pigmentation over her face and shoulders. No adenopathy was noted. The heart and lungs were normal. The blood pressure was 110/60 mm. of Hg. The abdomen was scaphoid, with the spleen palpably enlarged to a level just below the umbilicus. It was smooth and nontender. The liver was enlarged three to four fingerbreadths below the costal margin, and felt smooth and regular. There were no bony abnormalities, and the reflexes were normal.

Laboratory Examination: The red blood count on admission was 3,450,000 per cubic millimeter, with a hematocrit of 33% and hemoglobin of 10 gm.%. The white blood count was 4,200 per cubic millimeter, with 57% polymorphonuclears, 38% lymphocytes, 4% monocytes and 1% eosinophils. The reticulocytes were 1.3%. Calculated blood indices were: MCV, 94; MCH, 29; MCHC, 30. Subsequent blood counts revealed a slight rise in the hemoglobin and hematocrit, but were always consistent with a mild anemia with mild leukopenia. The erythrocyte osmotic fragility was normal. Sickle cell preparation and smears for malaria were negative. The cephalin-cholesterol flocculation test was 1 plus in 48 hours, and there was no retention of bromsulfalein. Bleeding and coagulation times were within normal limits. Kahn test was negative. Urinalysis was negative for bilirubin, and showed urobilinogen in a dilution of 1:4. Bone marrow aspiration revealed a normoblastic hyperplasia with a M:E ratio of 1.2:1. Scattered large phagocytes typical of Gaucher's cells were noted. Splenic aspiration corroborated the diagnosis of Gaucher's disease. Roentgenograph of the chest was normal, and abdominal scout films demonstrated an enlarged liver and a markedly enlarged spleen. X-rays of the long bones were normal.

Course: The patient was given a 500 c.c. blood transfusion for her symptomatic anemia and discharged. She was re-admitted a few days later and underwent therapeutic dilatation and curettage. Splenectomy was contemplated for the near future.

The patient was readmitted April 17, 1951, at which time she was four months pregnant. Her spleen occupied the entire left upper quadrant, extending inferiorly to the left iliac crest. As she desired to carry her pregnancy to term, it was considered advisable to undertake splenectomy. The red blood count was 4,400,000, with 11 gm.% hemoglobin. The white blood count was 4,400, with 59% neutrophils, 33% lymphocytes and 8% monocytes. The platelet count was 110,000. Splenectomy was accomplished the following day. Platelet counts on blood from the splenic vein and splenic arteries revealed no significant difference. The spleen was firm and freely movable, and weighed 2,150 gm. The patient tolerated the procedure well and made an essentially uneventful recovery. The platelet count postoperatively rose

as high as 600,000. Five months later the patient delivered a normal, full term infant without complications. She was again admitted on January 18, 1953, at which time she had an uncomplicated delivery of a normal, full term, seven pound, four and three quarter ounce infant, followed by an uneventful puerperium.

A hemogram performed on April 21, 1955, revealed an erythrocyte count of 4,400,000, with a hemoglobin of 14 gm.% and a hematocrit of 45%. The leukocyte count was 11,200, with 47% neutrophils, 44% lymphocytes, 3% monocytes, 4% eosinophils and 2% basophils. Reticulocytes were 1% and platelets 33,000. The bleeding, clotting and clot-retraction times were normal.

Discussion

It seemed remarkable to us that not only did these identical twins harbor this rare entity, but also both had associated term pregnancies during the course of which splenectomies were performed. The occurrence of pregnancy in patients with Gaucher's disease deserves a few words of comment.

Groen [18] in his review stated that there is a high incidence of sterility and abortion in parents with Gaucher's disease and a high incidence of neonatal deaths in the offspring. It was felt, in both cases, that splenectomy was indicated early in the pregnancy because of the large size of the organ and its probable interference with the enlarging uterus. Bromberg, Toaff and Diengott [25] felt that the anemia, the splenomegaly, the often destructive bone changes, and the poor general condition of many of these patients may lead the obstetrician to consider termination of their pregnancy. They reported a study of seven Jewish women seen in the Hadassah University Hospital who had had 13 recorded pregnancies. Nine proceeded to term and four had therapeutic interruption during the first trimester because of the prevailing opinion among the Israeli obstetricians that pregnancy involved added risk for these patients. Four of the seven had one pregnancy, while the others had two, three and four pregnancies, all of which ended in full term deliveries. There were no spontaneous abortions, premature labors or toxemias. In spite of reduced platelet counts (in some as low as 60,000), there were no hemorrhagic complications. All the viable infants at term were normal, and there were no fetal deaths in utero. One delivery was complicated by a stillbirth of one of the twins. The enormous spleen size present in some did not interfere with the normal increase in size of the gravid uterus or with labor. They felt that there were no adverse effects on the basic disease process, and that women affected with Gaucher's disease should not be deprived of motherhood.

Anemia complicating pregnancy in Gaucher's disease was reported by Elliott,[26] who cited the case of a 25 year old female first seen during pregnancy with a marked hypochromic anemia and splenomegaly suggesting Banti's disease. Before she was able to receive transfusions planned for her at term, she gave birth to an apparently normal, though premature, infant. In spite of multiple postpartum transfusions her anemia slowly recurred, and a repeated bone marrow study suggested Gaucher's disease, which was confirmed following splenectomy. Her anemia, considered to be on a hypersplenic basis, improved following surgery.

Splenectomy for Gaucher's disease was first performed in 1895 on a woman operated upon for a suspected uterine fibroid.[27] Erdmann and Moorhead [28] summarized 10 cases that had been splenectomized by 1914, with two postopera-

tive deaths. Gordon [29] stated that the principal objection to splenectomy has been the reported high mortality, but that the Gaucher's spleen, although often of huge size, is one of the easiest to remove, as it is rarely adherent. He felt that the mortality should be well under 20%. While Pick [30] and many others felt that the splenectomy hastened the onset and spread of osseous involvement, Logan [31] and others did not support this contention. All seemed to agree that splenectomy has definite palliative value in that it improves the anemia, corrects the hemorrhagic diathesis and frees the patient of the burdensome weight of a tremendously enlarged organ.

The anemia and hemorrhagic diathesis are usually attributed to manifestations of a secondary hypersplenism, and the red blood cells and platelets can be expected to rise after surgery. Davis et al.[32] reported "selective" hypersplenism, manifested by a thrombocytopenia only, with return to normal levels after splenectomy. Logan [31] suggested that splenectomy, in addition, increases the resistance to infection of these patients. This may be due in part to the rise in the white blood cells, which are often at leukopenic levels prior to splenectomy, as evident in many reported cases.[28, 31, 33] It is interesting to note that, of the 29 cases reviewed by Medoff and Bayrd,[33] representing all those cases of Gaucher's disease seen at the Mayo Clinic up to and through 1950, 15 underwent splenectomy, with two postoperative deaths. Follow-up studies revealed that six of the splenectomized patients were alive 11 to 20 years after surgery.

Other modalities have been utilized in the past in an attempt to reduce the size of the spleen or correct the hematologic aberrations. Roentgen therapy to the spleen has been universally unsuccessful. Decker and McWhorter [24] employed cortisone therapy in one of their cases and reported success in improving the anemia and gaining a partial remission of the leukopenia. Little effect, however, was noted on the low thrombocyte level or bleeding tendency.

With all these considerations in mind, coupled with the experience of Bromberg et al.,[25] it would appear that pregnancy alone is not an absolute indication for splenectomy. Every case should be evaluated individually, with due consideration being given to the combined spleen and liver size, status of the hematopoietic system and general condition of the patient. Since we are now in the popular "hypersplenism" era, it is not unlikely that splenectomy will be performed with greater frequency in patients suffering from this disease, especially when the hematopoietic alterations are of such magnitude as to interfere with the otherwise well-being of the patient.

Summary

1. The heretofore unpublished occurrence of Gaucher's disease in identical twins is reported, and the familial and hereditary aspects of this disease are reviewed.

2. The coincidental occurrence of pregnancy in Gaucher's disease and the role of splenectomy are discussed.

Acknowledgment

The authors are indebted to Dr. B. Decker and Dr. A. McWhorter for permission to utilize the clinical records on case 2 of this paper.

Summario in Interlingua

Morbo de Gaucher es un rar disordine familial, characterisate per un disturbation del metabolismo de cerebrosido, con immagasinage o retention anormal de cerasina in le cellulas del systema reticulo-endothelial. Le classic constatationes clinic es splenomegalia, pingueculas, pigmentation symmetric, moderate grados de anemia con leucopenia, e un deformitate a contorno de "phiale de Erlenmeyer" del humero distal.

Le aspectos hereditari e familial de iste morbo attraheva primo le attention de investigatores in 1895, quando Collier reportava su occurrentia in sorores. Solmente le diffusion horizontal del morbo—i.e. su occurrentia multiple in membros de un sol generation—esseva cognoscite ante 1948. Tamen, in 1949 Green addeva duo casos de diffusion vertical, le un de un patre e duo filios de ille e le altere de un patre e duo filias. Le hypotheses avantiate pro explicar le mechanismo genetic del morbo ha stipulate un passage como simple tracto dominante e como autosomal tracto recessive. Le presente articulo contribue un reporto del occurrentia de morbo de Gaucher in geminos identic. Nulle tal ha previemente essite publicate.

Le absentia de effectos adverse in le morbo in consequentia de pregnantias e le remarcabilemente non-complicate curso del gestation e del parturition es nove elementos a considerar in le planation del therapia de patientes con iste morbo. Le experientias de Brombert et al. in Israel es notabile in iste respecto.

Il non existe un therapia specific, sed transfusiones e splenectomia es empleate le plus frequentemente como mesuras palliative. Le majoritate del investigatores es de accordo que splenectomia succede frequentemente a meliorar le anemia, a corriger le diathese hemorrhagic, e a liberar le patiente ab le moleste peso de un tremendemente allargate organo. Steroides ha recentemente essite instituite pro alleviar le cytopenia general o selective. Il pare que pregnantia per se non es un indication absolute pro splenectomia, e omne possibile aberration hematologic debe esser evalutate cautemente ante que un intervention chirurgic es executate.

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PROGRESSIVE EXOPHTHALMOS DEVELOPING 12 YEARS AFTER THYROIDECTOMY FOR DIFFUSE TOXIC GOITER*

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ENDOCRINE exophthalmos can occur with or without evident hyperthyroidism, or may develop only after therapeutically induced remission of the thyrotoxicosis. The cause of the disorder has not been completely explained, but a pituitary factor, either thyrotropin or a physiologically related substance, is thought to be involved in its pathogenesis. The unusual history is presented of a patient who developed severe infiltrative ophthalmopathy 12 years after thyroidectomy. The normal pituitary-thyroid relationship associated with the exophthalmos is a significant feature of the case study.

CASE REPORT

A 62 year old housewife was first examined at the Henry Ford Hospital in January, 1957, because of progressive swelling of the eyelids for two months. The swelling, which was most prominent in the morning, was associated with redness of the eyes and tearing, but there was no itching, burning or discharge. Since the onset of these symptoms the patient had felt more nervous and tired than usual. Involvement of her son in a minor car accident the previous summer had caused her considerable emotional upset, and she "hadn't slept in months." Twelve years previously the patient had undergone thyroidectomy for toxic diffuse goiter at another hospital. Convalescence had been uneventful, with no observed eye complication.

The patient was a moderately obese white woman who appeared tense and anxious. The most striking physical feature was the marked, soft, baggy, noninflammatory edema of the upper and lower eyelids bilaterally, associated with conjunctival hyperemia and edema (figure 1). There was limitation of both vertical and horizontal movements of the eyes, but no apparent proptosis or lidlag. Hertel exophthalmometer readings were 20 mm. in both eyes, moderately over the limits of normal.

The trachea deviated to the right under the thyroidectomy scar, and a small mass of firm, irregular tissue was palpable in the area of the left upper pole of the gland. The cardiac rhythm was regular, with 88 beats per minute, and the blood pressure was 180/86 mm. of Hg. The texture of the skin and hair was normal, and there was no excess perspiration. The patient had no tremor or muscular weakness.

The basal metabolic rate was ± 0. The 24-hour uptake of I^{131} was 36% of a 10 microcurie test dose, which was shown by means of a scintigram to be concentrated in the small remnant of the left thyroid lobe. The patient was given sedatives and increasing doses of sodium l-thyroxine, beginning with 0.1 mg. daily. The dose was increased to 0.2 mg. daily the second week, and to 0.3 mg. daily thereafter. Three weeks after initiation of thyroxine therapy the 24-hour I^{131} uptake had been reduced from 36% to 10%.

Administration of thyroxine, 0.3 mg. daily, was continued until the patient developed mild symptoms of hyperthyroidism, necessitating a reduction in dosage.

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During the four months of observation there has been no reduction in periorbital edema or regression of exophthalmos, although the size of the remnant of thyroid tissue has diminished appreciably. Localized pretibial myxedema, most marked on the left leg, developed four months after the onset of the ophthalmopathy and has persisted to this time.

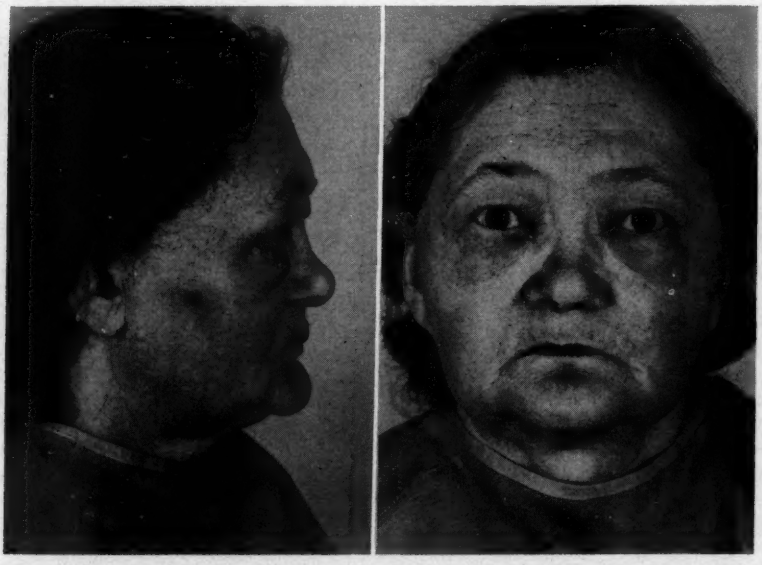

FIG. 1. Infiltrative ophthalmopathy (exophthalmometer reading, 20 mm.), which had its onset 12 years after thyroidectomy for toxic diffuse goiter.

DISCUSSION

A recent report of 74 patients in whom exophthalmos was the predominant clinical feature indicates that 33 were hyperthyroid, 25 euthyroid and 16 hypothyroid at the time the condition was first observed.[1] Some of these patients developed exophthalmos soon after operation for toxic goiter. In two, the condition occurred 12 and 14 years after surgery, without appreciable concomitant thyroid dysfunction, while a third developed exophthalmos with mild recurrent hyperthyroidism 10 years after operation. In the 10-year period just preceding the introduction of antithyroid drugs, 115 of approximately 1,500 patients with toxic diffuse goiter observed at the New York Presbyterian Hospital had eye changes.[2] Severe infiltrative ophthalmopathy occurred in 15 patients, three of whom developed the disorder several years after successful treatment for hyperthyroidism. These three were in the older age group.

In recent years, radioactive iodine tracer technics have been utilized to develop accurate procedures for the evaluation of thyroid function and pituitary-thyroid relationships. By this means it has been shown that endogenous thyroid function in normal subjects is markedly depressed by the administration of adequate daily physiologic doses of thyroid hormone.[3] Several studies have dem-

onstrated that the administration of desiccated thyroid [4, 5] or tri-iodothyronine [5, 6, 7] does not suppress the thyroidal uptake of I^{131} of hyperthyroid patients, whereas these substances markedly decrease I^{131} uptake in euthyroid controls. This failure of the thyroid gland to respond to the administration of desiccated thyroid or tri-iodothyronine with a diminished I^{131} uptake is widely used as a simple, reliable test for the diagnosis of hyperthyroidism.

Werner recently reported the response to tri-iodothyronine of 10 euthyroid patients with the early eye signs of Graves' disease.[8] Thyroidal I^{131} uptake was determined before and after the administration of 0.07 to 1 mg. tri-iodothyronine daily for eight days. The failure to decrease thyroidal I^{131} uptake in this group was striking in contrast to the markedly decreased uptake of 30 euthyroid control subjects after similar treatment. Thyrotropin administration to these patients with early eye signs produced a brisk increase in serum protein-bound iodine, although the I^{131} uptake was only slightly enhanced. Thus, the response of these patients to tri-iodothyronine and thyrotropin was similar to that of subjects with Graves' disease, indicating that they do, in fact, have this disorder. Although the euthyroid state was maintained, the pituitary-thyroid relationship was abnormal.

Interpreting the failure of I^{131} uptake to decrease significantly after tri-iodothyronine administration as an indication of persistent disease within the thyroid remnant, Werner has shown that the disordered activity can persist more than 20 years after therapy-induced remission of hyperthyroidism.[9] On the other hand, the disturbance may subside within a few months. The thyroid function of most patients treated with radioactive iodine was abnormal for at least five years after therapy. By contrast, the functional disturbance subsided within two years in most surgically treated patients.

The patient who is the subject of this report developed progressive exophthalmos 12 years after subtotal removal of a toxic diffuse goiter. When first examined for the eye complaints she appeared to be euthyroid. This impression was confirmed by the normal basal metabolic rate and the 24-hour thyroidal I^{131} uptake of 36%. Surprisingly, endogenous thyroid activity was markedly decreased by the administration of physiologic doses of thyroxine, as shown by a fall of radioactive iodine uptake to 10%. This normal response to administered thyroid hormone is further evidence of the euthyroid state, and indicates that the original functional disturbance had neither persisted nor recurred in the remaining thyroid tissue. The normal response of our patient to the administration of thyroid hormone contrasts sharply to the reported abnormal response of euthyroid patients with the early eye signs of Graves' disease. Since thyroxine administration to this patient induced a marked decrease in thyroid function, it is concluded that the normal pituitary-thyroid relationship had been restored. In this case, therefore, it is quite unlikely that excess thyrotropin could be a factor in the development of the infiltrative ophthalmopathy. The study supports the concepts that a separate exophthalmos-producing factor is operative in the pathogenesis of this disorder, and that elaboration of this factor, which is also incriminated in the development of circumscribed pretibial myxedema, is unaffected by the level of thyrotropin or thyroid hormone.

SUMMARY

The development of severe infiltrative ophthalmopathy and localized pretibial myxedema 12 years after subtotal resection of a toxic diffuse goiter suggests that the physiologic disturbance of Graves' disease had either persisted or recurred. However, the patient was euthyroid and responded to the administration of thyroxine with a normal decrease in thyroid function, demonstrating an intact pituitary-thyroid relationship. This evidence is interpreted to indicate that the exophthalmos-producing factor is not thyrotropin, and is independent of both thyrotropin and thyroid hormone levels.

SUMMARIO IN INTERLINGUA

Le exophthalmia progressive del morbo de Graves es generalmente considerate como producto de un factor pituitari. Si o non le substantia exophthalmogene es identic con hormon thyroido-stimulatori remane un question controverse. Es reportate le caso de un patiente qui disveloppava sever ophthalmopathia infiltrative 12 annos post thyroidectomia pro struma diffuse toxic. Co-existeva myxedema pretibial, sed le patiente esseva euthyroide secundo le resultatos de tests clinic e laboratorial. Le administration de thyroxina produceva un grado significative de suppression de hormon thyroido-stimulatori. Isto se manifestava in un reduction del acceptation de I^{131} intra 24 horas ab 36% usque a 10%, lo que indicava etiam un normal relation pituitari-thyroide. Le administration continue de thyroxina durante un periodo de quatro menses resultava in nulle melioration del ophthalmopathia o in le myxedema pretibial, ben que le remanente histos thyroide esseva significativemente reducite in massa. Es concludite que le substantia exophthalmogene es distincte de thyrotropina, e su elaboration es independente del nivello de hormon thyroido-stimulatori o de hormon thyroide in le circulation.

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EDITORIAL

PROGRESS REPORT

COMMITTEE FOR THE STUDY OF HOSPITAL STANDARDS IN MEDICINE

Conducted under a grant to The American College of Physicians by the Division of Hospital and Medical Facilities, Department of Health, Education and Welfare, Washington, D. C.

THIS study began in 1956 with the appointment of the Committee by the Regents of The American College of Physicians. The work of the Committee under its original Director, Dr. M. A. Blankenhorn, is described in some detail in a guest editorial that appeared in this journal.[1] As a result of this pioneering effort, the Committee reached three major conclusions: (1) that the quality of care in any hospital may be judged by the careful evaluation of certain records; (2) that an examination of the staff organization of any hospital may be helpful in judging the quality of medical care; (3) that an inside audit, with particular reference to hospital deaths, is the method most likely to maintain high standards of practice.

Dr. Arthur Colwell, Chairman of the Committee, in a report to the Regents in April, 1957, expressed regret that no magic formula for judging the quality of medical care had appeared, and he stated his belief that the results up to that time were quite inconclusive. It is true that no magic formula had appeared, but the result of the early part of the study allowed us to focus more sharply upon the most promising leads.

In planning the work of the current year, the Committee decided to concentrate on an investigation of the so-called "inside audit." We prefer the term "internal appraisal." The term "audit" is usually applied to a procedure that examines for accuracy and completeness. Most hospitals have some sort of record audit that is designed to examine the record in this manner. By "internal appraisal" we mean the efforts of an individual staff to judge the quality of its own work by critical examination of hospital records of selected patients.

To this end, the Director wrote to all of the hospitals that coöperated in the initial survey under Dr. Blankenhorn and to an additional 109 hospitals throughout the country. Each hospital was asked whether an internal appraisal system was employed. We asked for permission to visit these hospitals and for the coöperation of the "chief of medicine" of the hospital. Of more than 200 hospitals, none refused to coöperate. Eighteen

[1] Blankenhorn, M. A.: Standards of practice of internal medicine and methods of assessing the quality of practice in hospitals (editorial), Ann. Int. Med. 47: 367–374 (Aug.) 1957.

hospitals failed to reply, but all that did expressed willingness—indeed, eagerness—to coöperate. A surprising number (about 55%) indicated that an internal appraisal existed in one form or another. The Director then enlisted the aid of some 20 members of the College to act as surveyors.[2] Many had participated in the survey of the previous year and agreed to act again. Others participated for the first time and were friends of the Director or were recommended by officers of the College or by former surveyors. Each member of the Committee was asked to visit and study at

TABLE 1

Statistics

Number of hospitals that have received letters from the Committee since May 1, 1957	214
Number of above hospitals that have been surveyed previously	105
Number of above hospitals approached for the first time this year	109
Number of hospitals failing to reply to letter	18
Number of hospitals assigned to surveyors	105
Number of hospitals surveyed in last year's study	43
Number of hospitals not previously surveyed	62
Total number of surveyors	25
Number of men who surveyed hospitals last year	14
Number of surveyors without previous experience	11
Total number of hospitals that indicated they used an internal appraisal system	118
Of the 105 hospitals assigned to surveyors, number which indicated they used an internal appraisal system	78
Number of hospitals surveyed which had:	
Residents, interns and a teaching affiliation	11
Residents and interns	43
Residents only	8
Interns only	7
No house staff	17

least one hospital. The Director then selected approximately 100 hospitals from the current list of 214. Some of them had been studied in the previous year; others were visited for the first time. All were general hospitals of 100- to 600-bed capacity. Some had teaching affiliation, many had house staff, and some had neither. Data concerning hospitals and surveyors appear in table 1.

Surveyors were supplied with survey forms. Each was asked to visit several hospitals, with a maximum of five for any one man. Each surveyor

[2] The Committee: Arthur R. Colwell, M.D., Chairman, Chicago, Illinois; Ellsworth L. Amidon, M.D., Burlington, Vermont; Fuller B. Bailey, M.D., Salt Lake City, Utah; C. Wesley Eisele, M.D., Denver, Colorado; E. Hugh Luckey, M.D., New York, New York; Karver L. Puestow, M.D., Madison, Wisconsin; G. Karl Fenn, M.D., Director, Chicago, Illinois.

The Surveyors: Alex M. Burgess, Sr., M.D., Providence, Rhode Island; Thomas J. Coogan, M.D., Chicago, Illinois; Hugh L. Dwyer, M.D., New Haven, Connecticut; Max L. Garon, M.D., Louisville, Kentucky; William J. Grace, M.D., New York, New York; Julian Kaufman, M.D., Fort Wayne, Indiana; Joseph D. McCarthy, M.D., Omaha, Nebraska; Frank B. McGlone, M.D., Denver, Colorado; Lawrence T. Minish, Jr., M.D., Louisville, Kentucky; Jack O. W. Rash, M.D., Miami, Florida; Edward H. Reinhard, M.D., St. Louis, Missouri; Truman G. Schnabel, Sr., M.D., Philadelphia, Pennsylvania; Maurice A. Schnitker, M.D., Toledo, Ohio; J. James Smith, M.D., New York, New York; Franz H. Stewart, M.D., Miami, Florida; Maurice B. Strauss, M.D., Boston, Massachusetts; Henry E. Wilson, M. D., Columbus, Ohio; R. Hugh Wood, M.D., Atlanta, Georgia.

was asked to fill out a survey form and return it to the Director. He was asked to give his over-all opinion of the quality of medical care received by patients in each hospital. In addition, he was asked to make a narrative report, with comments and suggestions concerning the quality of internal medicine practice in the hospitals visited.

THE AMERICAN COLLEGE OF PHYSICIANS
STUDY OF HOSPITAL STANDARDS IN MEDICINE

.....**Hospital** .....**City**

INTERNAL APPRAISAL

By "appraisal" is meant exercise of critical judgment concerning the quality of internal medicine practice (not the quality of record keeping) as performed by individual physicians on the hospital staff. By "internal appraisal" is meant the exercise of such judgment by designated members of the staff itself.

By whom done?

Are all records examined or only certain ones?

How selected?

How frequently done?

Are causes of death examined and discussed by the staff?

Is written report of deficiencies made? If so, to whom?

Action taken?

In your opinion, is this type of appraisal effective and does it tend to elevate standards of practice in this hospital?

FIG. 1.

A survey form was designed to develop those points that promised to be of the greatest importance. It consisted of a four-page leaflet. Page 1 requested information concerning the internal appraisal system, if any, already employed by the hospital. After careful evaluation, the surveyor was asked to state whether the existing system improved the standards of practice in that hospital, and to what extent (figure 1). Page 2 contained

questions which could be answered by the medical record librarian. These were designed to obtain information by which the quality of staff organization might be judged (figure 2). Page 3 was an outline for the critical evaluation of the treatment of patients in certain disease categories. It

.....Hospital .....City

DATA OBTAINED FROM RECORD LIBRARIAN

1. Is your pathologist on full time or part time basis?
   If part time, how much time?

2. Is your radiologist on full time or part time basis?
   If part time, how much time?

3. What is your autopsy percentage in Medicine for past year?

4. What is the numerical relation between the number of written consultations and the number of admissions during the past year?

   For example: $\frac{\text{Number of written consultations}}{\text{number of admissions}}$ represents the percentage of consultations for the entire staff.

5. Number of scientific (not business) meetings held by staff during past year.

   Entire Staff_____

   Department of Medicine, if separate_____

6. Percentage of members of staff practicing internal medicine who are certified by

   American Board of Internal Medicine_____

   American Academy of General Practice_____

FIG. 2.

was demonstrated in the first year of this study that an experienced internist can evaluate the quality of medical care with a fair degree of accuracy in any hospital. He formed his opinion by a visit to the hospital, where he received a general impression. A critical examination of certain records was a very important factor in the formation of his opinion (figure 3).

Page 4 of the survey form contained space for the surveyor's opinion

of the general over-all quality of care received by patients in each hospital. We were hopeful that we might be able to show a correlation between the evaluation of the surveyor obtained from page 3 and the information obtained from pages 1 and 2.

DATA OBTAINED FROM RECORDS

CARDIAC DISEASE

Failure:

Low sodium diet used?

What diuretics were used?

Was intake and output measured?

How often was patient weighed?

Coronary Occlusion:

Were serial ECGs used?

How often was white count done?

Was sedimentation rate or transaminase observed?

How often was prothrombin time observed?

DIABETES

Was retinal examination done on all diabetics?

If not, what proportion?

Was plasma CO_2 determined in coma and pre-coma?

How often?

In coma and pre-coma what was the average insulin dosage during first six hours?

GASTROINTESTINAL DISEASE

Was proctoscopic done on all G.I. patients?

If not, what proportion?

Were stools examined for blood, amoeba or bacteria?

What liver function tests were used?

How often were blood counts made in bleeding peptic ulcer?

BLOOD AND/OR COLLAGEN DISEASE

How often were complete blood counts made?

How often were platelet counts made?

Was sternal marrow biopsy done?

Was LE cell preparation studied? C reactive protein?

Was tissue biopsy done?

FIG. 3.

Based on the reports of the surveyors, the care in each hospital was graded as excellent, good, fair or poor. Excellent represented outstanding performance; good, better than average, but not outstanding; fair, that twilight zone between average and unacceptable; poor, quite unacceptable. Using the surveyor's over-all grade as the measuring stick, the hospitals fell into the following classes: excellent, 21%; good, 41%; fair, 31%; poor, 7%.

An attempt to correlate these grades with the information obtained from page 2 of the survey form was unsuccessful. This information, which was assembled at the hospital prior to the surveyor's visit, could be used only as a rough index of the quality of care. The quality of care in a particular hospital may not be judged in this manner. The narrative reports of the surveyors showed that a well organized hospital staff under good supervision was almost invariably accompanied by a high quality of care. This survey failed to disclose a method of determining the quality of staff organization in any hospital without depending upon the opinion of an experienced internist who had visited the hospital.

The information obtained from Page 1 of the survey form was much more encouraging. It was the unanimous opinion of the surveyors that an internal appraisal system was most important in maintaining and elevating the quality of medical care. Even when the system was relatively ineffective, the quality of care was found to be better than where no such system existed. Seventy-eight of the 105 hospitals that were visited indicated that they employed an internal appraisal system. The survey discloses many interesting facts relative to these systems. One striking fact concerns some of the hospitals that stated that no internal appraisal system was employed. Several such hospitals had a record of excellent performance. Investigation showed that these were teaching hospitals with university affiliation, or that they were hospitals with a tightly organized staff structure. In both cases the quality of care was being appraised constantly, although there was no formal system for so doing. In a few instances, a hospital had a teaching section which was separated, staffwise, from the private patient section. Invariably, the quality of care in the teaching section was superior to that in the private patient section. In other hospitals, where there actually was no appraisal system, the quality of care varied tremendously. While there was evidence of a high quality of care in many such hospitals, there were far too many instances of poor, or at least uncritical, practice. It is clear that poor practice may exist without detection unless some method of evaluation is employed. There were too many instances of "an excellent record, but mediocre care." There seemed to be no mechanism by which the staff could judge or be aware of its own standards.

Three types of appraisal were found in the hospitals that purported to employ such a system. The most common was little if anything more than a record audit. The record was examined to be sure it fulfilled certain record-keeping requirements, but no effort was made to evaluate medical care. Usually, these were incomplete records that were selected by the record librarian. Thus, the Committee had the opportunity to examine only incomplete records, and its job was to see that the offending physician completed the record. The Committee feels that this system, important as it is, does not contribute heavily enough to the maintenance of high standards of practice. At best, it may improve the record-keeping of chronic offenders.

Many hospitals made an effort to evaluate the quality of care but attempted the impossible task of examining every record. The result was a careful evaluation of relatively few records, and these involved physicians whose methods of practice were under suspicion or who were candidates for disciplinary action. The findings in such cases were reported to the chief of medicine or to the executive committee. Sometimes the committee or its chairman dealt directly with the offending physician. No information was returned to the staff concerning the general quality of its work. We feel that the value of such an appraisal is limited. The quality of care may be improved by the mere knowledge that some sort of appraisal is being done.

The third type of appraisal utilized a variety of methods, but all pointed to the same objective. This appraisal thoroughly evaluated a fair sample of the records without attempting to examine all of them. It sought, rather, to evaluate some records of each physician. The appraisal committee was an informative body, not a punitive one. It attempted to bring back information to the staff relative to the general quality of its work, without citing specific patients or physicians.

After an examination of all of the material concerned with internal appraisal systems, the Committee is convinced that the presence of an effective system will not only maintain high standards of practice but will also elevate these standards where necessary. The Committee believes that a uniform appraisal system should be used throughout the country. This will permit more rapid perfection of an appraisal plan and will ultimately permit the Joint Commission, if it chooses to do so, to evaluate the quality of medical care in any hospital by the effectiveness of the appraisal system in that hospital.

No uniform appraisal plan is in use today. Many of the surveyed hospitals have asked for help in developing an appraisal system for their own use. The Committee believes a plan should be made available to these hospitals and, indeed, to any hospital which desires to use it.

Using all of the material collected in the survey, and depending particularly on the narrative reports of the surveyors, the Director constructed a "Medical Care Appraisal Plan" that may be used in any hospital. This plan was presented before a meeting of the Committee. The Committee discussed, criticized and edited the plan. It meets all of the conditions that we can foresee, but there is no doubt in the mind of the Director that this plan may be improved by a trial in the field. No plan should be taken from the drafting board and recommended for use without such a trial. "The Medical Care Appraisal Plan," accompanied by an appraisal form devised by the Committee, is now ready for such a trial.

G. Karl Fenn, M.D.,
Director,
Study of Hospital Standards in Medicine

REVIEWS

An Introduction to Medical Mycology. 4th Ed. By GEORGE M. LEWIS, M.D., Professor of Clinical Medicine (Dermatology), Cornell University Medical College, Ithaca, New York; MARY E. HOPPER, M.S., Research Fellow in Medicine, Cornell University Medical College; J. WALTER WILSON, M.D., Clinical Professor of Medicine, University of Southern California, Los Angeles, California; and ORDA A. PLUNKETT, Ph.D., Professor of Botany, University of California at Los Angeles, Los Angeles, California. 453 pages; 18 × 26 cm. 1958. The Year Book Publishers, Inc., Chicago. Price, $15.00.

The new edition of this book has been completely revised and reorganized under a broadened authorship and, in format, bears little resemblance to its predecessors. Previous editions treated the clinical and laboratory aspects of the various mycoses in separate chapters. The present volume does not separate them. This is an improvement. The chapter dealing with the fundamentals of elementary mycology is quite adequate, and though many terms are italicized and defined through usage, this reviewer feels there is still a need for a glossary. However, the authors may feel that their many excellent illustrations depicting fungal structures preclude the necessity for that "defined list of terms" which is a valued component of many introductory texts.

Chapter one introduces the reader to the superficial mycoses and here a plea is made, on the basis of the relative simplicity of mycologic diagnostic methods, for the serious worker to think along etiologic as well as clinical lines when rendering a diagnosis. Here, too, as in the preface, supported with logical reasoning, is an expression of disapproval for the continued use of such time-honored terms as: tinea barbae, tinea capitis, tinea corporis, etc. In keeping with the etiologic approach superficial mycoses dealt with in subsequent chapters are, for the most part, referred to as: microsporoses, trichophytoses, or epidermophytosis depending upon the dermatophyte involved rather than upon the region or structure of the body involved.

The increasing incidence, whether it be real or apparent, of *Candida albicans* infections makes the chapter on candidiasis in a medical mycology text extremely important today, particularly where differential diagnosis is concerned. To say merely that other members of the *Candida* genus ". . . may be distinguished from *Candida albicans* by the absence of chlamydospores when they are grown on corn meal agar" is an over-simplification. Indeed, it is a common occurrence to isolate strains of *C. albicans* which do not form a mycelial growth on corn meal agar. Currently, there is a real need for better selective and differential media for the isolation and identification of *C. albicans* than are in common use.

Prior to the consideration of the deep mycoses, there are chapters dealing with the physiology and nutritional requirements of the dermatophytes, the immunology and allergic reactions of the dermatophytes, and the treatment of the superficial mycoses. Of particular interest are the discussion and tabulation of data on the trichophytin skin test. Because of its specificity and the significance of a positive reaction, a good case is presented for its value as a diagnostic tool where dermatophytoses and dermatophytids are suspected. Oidiomycin, on the other hand, is shown to be of little value in the diagnosis of *C. albicans* infections. Of timely interest are the data showing a conjoint sensitization between penicillin and the dermatophytes. Interesting, also, is the brief discussion on air-borne fungi as allergens.

The chapters on the deep mycoses are organized as follows: history, etiology, distribution, epidemiology, clinical characteristics, pathology, mycology, immunology, differential diagnosis, prognosis and treatment. Under these headings information

is clearly and concisely presented and, furthermore, is supported by extensive bibliographies. In addition to the excellent photographic figures of the clinical and cultural aspects of these mycoses, there is associated with the mycology section of each chapter a line drawing illustration showing the characteristic morphologies of the culture and tissue phases. This is a helpful component since we are dealing here, for the most part, with dimorphic fungi. Very little consideration is given to such fungus infections as mucormycosis, geotrichosis and aspergillosis.

The immunology and allergy associated with the deep mycoses are epitomized in one and a half pages and this is probably adequate treatment considering the present state of our general knowledge in this area. A chapter on fungus diseases in relation to workmen's compensation, likewise, is very short, but thought-provoking. Also concisely presented is a general discussion on methods of diagnosis. Not so concise, and very valuable, is the chapter on laboratory methods.

Past editions have established "An Introduction to Medical Mycology" as a classic in its field. The fourth edition maintains this status. Its wide coverage, its lucid exposition, its excellent illustrations, both clinical and photomicrographic, and its authoritative authorship provide a firm foundation for such an evaluation. It is to be recommended to all who have any interest in medical mycology.

ANDREW G. SMITH

Drugs of Choice. Edited by WALTER MODELL, M.D., Associate Professor of Pharmacology, Cornell University Medical College. 931 pages; 17.5 × 25.5 cm. The C. V. Mosby Co., St. Louis, Mo. 1958. Price, $12.75.

Dr. Modell has succeeded in getting a number of capable clinicians to combine their efforts in various fields of medical practice in order to write an unusual text entitled "Drugs of Choice."

The first chapter, written by the Editor, deals with the principles of choosing drugs for various clinical entities. Problems of pharmacology, statistical evaluation, use of placebos, dosage schedules, and other important criteria of the parameters of drug action are discussed in this important chapter.

There are 34 additional chapters which in the reviewer's opinion cover most of the fields of medical practice requiring drug therapy. Some of these are excellently written and complete in their coverage of the subject, such as the one on "The Choice of Drugs for Hematologic Disorders" by William McFarland and William Dameshek, and "The Choice of Drugs for Diseases of the Heart" by the Editor. Some of the chapters are less adequate in the coverage of their subject, and like any other symposium of this kind there is a tremendous variation in approach to the various divisions of medicine and also in the style of diction.

In the main this text goes beyond many of the textbooks in pharmacology in setting forth the drug of choice for many diseases and supporting this with adequate clinical background. In addition, the book contains selected references and to each chapter is appended a drug index listing pharmaceutical preparations with generic and trade names, also the company making them available.

JOHN C. KRANTZ, JR.

Shock and Circulatory Homeostasis: Transactions of the Fifth Conference, November 30, December 1 and 2, 1955, Princeton, N. J. Edited by HAROLD D. GREEN, M.D., D.Sc. 337 pages; 15.5 × 23.5 cm. Sponsored by the Josiah Macy, Jr. Foundation, New York. 1957. Price, $4.75.

This monograph reports the transactions of the Fifth (1955) Josiah Macy sponsored conference on Shock and Circulatory Homeostasis. Emphasis is given to the controversial problem of the significance of the bacterial factor in shock. Individual sections are devoted to a description of hemorrhagic shock in germ-free

rats, the mechanism of the protection afforded by Aureomycin against shock, and certain studies implicating the participation of bacteria and their products in experimental shock. The section devoted to humoral factors presents additional evidence against the ferritin (VDM) hypothesis of irreversible shock. Another section analyzing the effect of a modified adrenergic blocking agent, G-D 131, is of interest but is largely centered about the ferritin hypothesis. The effects of adrenergic, anticholinergic, and ganglionic blockading agents and of hypothermia and chlorpromazine during experimental shock are discussed in detail; the debate as to mechanism of action should be of special interest to the vascular physiologist. Alterations in hepatic blood flow and mesenteric lymphatic flow during shock are also considered along with a comprehensive review of the anatomy of the portal circulation.

Although these documented discussions are invaluable to the investigator interested in the shock syndrome, they will be of interest also to the physiologist, the internist, and the surgeon. Concepts in the field of shock alter rapidly and certain portions of the text are already outdated by subsequently published experimental data. Nevertheless, the book remains a comprehensive review of some of the latest contributions to the understanding of circulatory homeostasis.

S. E. G.

Coronary Heart Disease: Angina Pectoris; Myocardial Infarction. By MILTON PLOTZ, M.D., F.A.C.P., Clinical Associate Professor of Medicine, State University of New York, Medical Center of New York. 353 pages; 18 × 26 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1957. Price, $12.00.

With the emergence of coronary heart disease as the major cause of death in this country and as an important cause of disability, there have been many papers, and more recently, a number of texts published on this important subject. In such a dynamic changing field, it is important that a text be up-to-date and comprehensive, yet have perspective and display good judgment with regard to both old and new concepts. This volume fulfils these criteria. It is lucidly and interestingly written. The illustrations and diagrams are good. The bibliography is selective and helpful. Much has been assembled in this book, which is recommended for use by internists, general practitioners and cardiologists.

SIDNEY SCHERLIS, M.D.

Neomycin, Its Nature and Practical Application. Edited by SELMAN A. WAKSMAN, HUBERT A. LECHEVALIER, BURTON A. WAISBREN and ROBERT A. DAY. 412 pages; 16 × 23.5 cm. Published for the Institute of Microbiology, Rutgers University, by the Williams and Wilkins Company, Baltimore. 1958. Price, $5.00.

This text on the nature and practical application of neomycin comes at a time when clinicians are witnessing therapeutic failures as a result of microbial resistance to various antibiotics. More than ever before, the usefulness of a potent drug such as neomycin is recognized and the clinician has been obliged to modify his thinking about the use of antimicrobial agents with certain obvious disadvantages. Thus, trepidation which formerly attended the use of neomycin has been diluted in part by the emergence of bacteria sensitive only to this antibiotic. The increasing use of neomycin has created a new need for information regarding its clinical application. Insofar as it is possible to answer the pertinent questions about neomycin, this book has done so.

Since 1949 when neomycin was isolated by Dr. Waksman and his associates there have been wide swings in the pendulum of popular opinion. At first, it appeared to be superior to streptomycin without its undesirable side effects and with a

broader spectrum of activity. Soon neomycin's devastating effects on auditory function became obvious as virtually everyone receiving long term therapy became deaf. This led to a restricted use of neomycin to those infectious disease problems which could be treated with local application of the antibiotic. Neomycin's efficacy in the preparation of bowel for surgery, enteric infections, wound infections and dermatoses, where absorption is limited, is well established. A large part of the section dealing with uses of neomycin is devoted to these types of clinical application. The successful treatment of bacterial peritonitis with intraperitoneal installation of neomycin is described. Although the results are impressive, few would argue that this is the method of choice except where neomycin is specifically indicated as in peritonitis associated with members of the genus *Proteus*. The use of neomycin in aerosol for chronic pulmonary disease has not been widespread but results suggest that further study along these lines is indicated.

Of greatest importance to the clinician is a definitive statement regarding indications for the parenteral use of neomycin. There are those infections, caused usually by gram-negative bacilli, which respond best to parenteral neomycin therapy. It is agreed that neomycin should be employed whenever in vitro resistance to other antibiotics has been demonstrated or other drugs have failed to control the infection. In neither case should the institution of neomycin therapy be attended by delay occasioned by fear of neurotoxicity. The use of neomycin at the rate of 1 gram daily for 7 days has, in the experience of these authors, not been associated with neurotoxicity or nephrotoxicity and such a treatment regimen is defined as maximal except in those instances where continued neomycin therapy is mandatory.

The various authors have concisely summarized available clinical experience with neomycin. In many instances the paucity of information is conspicuous and emphasizes the need for further careful evaluation of this antibiotic. While untoward effects of neomycin in man undoubtedly explain the apparent disinclination to employ this antibiotic in human infections, it does not excuse the deficiencies in our knowledge of the in vitro action of neomycin and its use in experimental infections as reported in the text. Frequently small numbers of certain species of bacteria have been tested for in vitro sensitivity to neomycin. The value of this limited experience is questionable when marked ranges in sensitivity are recorded and such a tabulation may even be misleading to the clinician who is not familiar with in vitro sensitivity testing methods. The absence of adequate information on body fluid concentrations of neomycin in man following parenteral administration is an obvious shortcoming and makes the interpretation of in vitro sensitivities even more difficult. The controversial issue of the etiology of hemorrhagic shock is an interesting one but is probably misplaced in a book of this type since the available evidence for or against this theory has all been derived from highly artificial experimental models using lower animals. The large amount of space devoted to biological aspects of *Streptomyces fradiae*, one of the sources of the neomycins, will probably detract from the appeal which this book will have for clinicians.

Notwithstanding these objections, this excellent summary of the available knowledge about neomycin will be a most welcome addition to the library of all of those concerned with antibiotics and the treatment of infectious diseases.

FRED R. MCCRUMB, JR., M.D.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

The Acute Abdomen. 2nd Ed. By WILLIAM REQUARTH, M.D., Clinical Assistant Professor of Surgery, University of Illinois College of Medicine; foreword by WARREN H. COLE, M.D. 313 pages; 20.5 × 14 cm. 1958. The Year Book Publishers, Inc., Chicago. Price, $6.50.

Advances in Internal Medicine. Volume IX, 1958. Editors: WILLIAM DOCK, M.D., State University of New York College of Medicine at New York City; and I. SNAPPER, M.D., Beth-El Hospital, Brooklyn. 311 pages; 23.5 × 15.5 cm. 1958. The Year Book Publishers, Inc., Chicago. Price, $8.50.

Collected Papers of The Mayo Clinic and The Mayo Foundation. Volume 49, 1957. Editorial Staff: CARL M. GAMBILL, A.B., M.D., M.P.H., JAMES R. ECKMAN, A.B., M.A., Ph.D., M. KATHARINE SMITH, B. A., FLORENCE L. SCHMIDT, B.S.E., GEORGE G. STILWELL, A.B., M.D., and GUY WHITEHEAD, B.A., M.A., Ph.D.; Senior Consultants: RICHARD M. HEWITT, B.A., M.A., M.D., and JOHN R. MINER, B.A., Sc.D.; compiled by GEORGE G. STILWELL, A.B., M.D. 827 pages; 24 × 15.5 cm. 1958. W. B. Saunders Company, Philadelphia. Price, $13.00.

Correlative Neuroanatomy and Functional Neurology. 9th Ed. By JOSEPH G. CHUSID, M.D., Attending Neurologist, St. Vincent's Hospital, New York; and JOSEPH J. MCDONALD, M.S., M.Sc.D., M.D., Dean of Medical Faculty, American University of Beirut, Beirut, Lebanon, etc. 344 pages; 25.5 × 17.5 cm. (paper-bound). 1958. Lange Medical Publications, Los Altos, California. Price, $4.50.

Diseases of the Esophagus. By J. TERRACOL, Professor of the Faculty of Medicine of Montpellier, France; and RICHARD H. SWEET, Associate Clinical Professor of Surgery, Harvard Medical School. 682 pages; 25.5 × 16.5 cm. 1958. W. B. Saunders Company, Philadelphia. Price, $20.00.

Electrocardiogram Clinics. By JOSEPH E. F. RISEMAN, M.D., Assistant Clinical Professor of Medicine, Harvard Medical School, etc.; and ELLIOT L. SAGALL, M.D., Instructor in Medicine, Harvard Medical School, etc. 259 pages; 24 × 31 cm. 1958. The Macmillan Company, New York. Price, $10.50 Ks.

Electrocardiography. By MICHAEL BERNREITER, M.D., F.A.C.P., Assistant Clinical Professor of Medicine, University of Kansas Medical School, etc. 134 pages; 23.5 × 18.5 cm. 1958. J. B. Lippincott Company, Philadelphia. Price, $5.00.

Etiology and Treatment of Leukemia: Proceedings of the First Louisiana Cancer Conference, Sponsored by Louisiana Division, American Cancer Society, Inc., Louisiana State University School of Medicine, Tulane University School of Medicine. Edited by WALTER J. BURDETTE, Ph.D., M.D., F.A.C.S., Professor and Head of the Department of Surgery and Director of the Laboratory of Clinical Biology, University of Utah College of Medicine, etc. 167 pages; 25.5 × 17.5 cm. 1958. The C. V. Mosby Company, St. Louis. Price, $4.00.

Expert Committee on Poliomyelitis: Second Report. World Health Organization Technical Report Series No. 145. 83 pages; 24 × 16 cm. (paper-bound). 1958. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, 60 cents.

Expert Committee on Water Fluoridation: First Report. World Health Organization Technical Report Series No. 146. 25 pages; 24 × 16 cm. (paper-bound). 1958. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, 30 cents.

Human Blood in New York City: A Study of Its Procurement, Distribution and Utilization, Conducted by the Committee on Public Health, The New York Acad-

emy of Medicine, under the direction of its Subcommittee on Blood Survey. H. D. KRUSE, M.D., General Director of Study. 147 pages; 21.5 × 14 cm. (paper-bound). 1958. The New York Academy of Medicine, New York.

Joint FAO/WHO Expert Committee on Brucellosis: Third Report. World Health Organization Technical Report Series No. 148. 51 pages; 24 × 16 cm. (paper-bound). 1958. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, 60 cents.

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